Global stability analysis of oseltamivir–resistant influenza virus model

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Abstract

We study a new model describing the dynamics of both Oseltamivir resistant and non-resistant Influenza virus. Incorporated in the model is oseltamivir drug for the non-resistant strain and nalidixic acid or dorzolomide drugs for the resistant strain. The basic reproduction ratios $R_0$ are determined using the next generation matrix. The local and global asymptotic stability of the disease free equilibrium are determined and shown to only exist if $R_0 \leq 1$ and $R_2 \leq 1$. Local and global asymptotic stability of the endemic equilibrium exist if $R_0 = 1$ and $R_2 = 1$. Lyapunov function was used to show the global stabilities.

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1. Introduction

Influenza viruses are segmented, negative-sense, enveloped RNA viruses. Influenza virus is of three types A, B and C. These types can be distinguished by serological responses to their internal proteins. Influenza A has antigenic variability which allows it to escape neutralization from antibodies. Influenza B also exhibits antigenic variability property, but less than that of A. This property is not common in influenza C, hence influenza A is more serious than B, and then C.

Influenza A virus is divided into hemagglutinin (H) and neuraminidase (N) based on the two proteins on the surface of the virus. Hemagglutinin are divided into eighteen types (H1 to H18) and neuraminidase into eleven
subtypes (N1 to N11). It can also be divided into different strains, most popular strains found in people are H1N1 and H3N2 viruses. The pandemic of influenza A (H1N1) reach its peak with the evolution of drug-resistant H1N1 strain.

Oseltamivir also known as Tamiflu is the most widely used anti-influenza drug. Nowadays, there is emergence of Oseltamivir-resistant H1N1 influenza viruses, which is as a result of natural genetic drift and drug treatment. Oseltamivir-resistant influenza virus can exist before or rapidly emerge during drug antiviral therapy. Ju Bao et al., proposed the use of drugs that are structurally similar to Oseltamivir as anti-Oseltamivir resistant influenza drugs. The drugs proposed are nalidixic acid and dorzolamide.

Mathematical models play vital roles in describing the transmission of both drug-resistance and non-resistance influenza viruses in a population. Most of these models are of the SEIR form. Global stability analysis of some of these models can be found in literature.

In this paper we consider a new SEIR model describing the dynamics of both oseltamivir resistance and non-resistance influenza. Incorporated in the model is the use of oseltamivir drug for the non-resistance virus and the use of nalidixic acid and dorzolamide drugs for the oseltamivir-resistance virus. Threshold quantities known as basic reproduction ratios and are found using next generation matrix. It is also shown that, if the disease free equilibrium is both locally and globally asymptotically stable and the disease dies out. Whereas if the endemic equilibriums are both locally and globally asymptotically stable and epidemics occur.

The paper is organized as follows: In chapter 2 the model is formulated, equilibria and basic reproduction ratios are also determined. Section 3 deals with local and global stabilities of DFE. Section 4 deals with local and global stabilities of the endemic equilibria. Conclusions are given in chapter 5.

2. Model Formulation

2.1. Construction of the Model

The transmission of both oseltamivir resistance and non-resistance influenza virus is considered. Also we incorporate the use of Oseltamivir drug for the non-resistance virus and the use of nalidixic acid and dorzolamide drugs for the oseltamivir-resistance virus. The population $N(t)$ is divided into six compartments by modifying the conventional SEIR model. The compartments are $S, E_R, I_R, E_u, I_u$ and $R$, which denotes the sizes of susceptible, infected but not infective oseltamivir-resistant, infectious oseltamivir resistant, infected but not infective non-resistant, infectious to non-resistant, and removed compartments respectively. We assume recruitment rate and natural death rate only in the susceptible compartment. The model is given by a system of ordinary differential equations:

$$\frac{dS}{dt} = \Lambda - \alpha SI_R - \beta SI_U - ds$$

$$\frac{dE_R}{dt} = \alpha SI_R - kE_R$$

$$\frac{dI_R}{dt} = k(1-p)E_R - \mu I_R$$

$$\frac{dE_U}{dt} = \beta SI_U - mE_U$$

$$\frac{dI_U}{dt} = m(1-q)E_U - \gamma I_U$$
\[ \frac{dR}{dt} = mqE_R + \gamma I_U + \mu d_R + kpE_R. \]

Where \( \Lambda \) is a constant recruitment rate and \( d \) is natural death rate which is only through the susceptible compartment, \( \alpha \) is a contact rate of oseltamivir-resistant virus, \( \beta \) is contact rate of non-resistant virus, \( kp \) and \( k(1-p) \) are the rate at which people that are exposed to oseltamivir resistant become recovered and infectious respectively, \( mq \) and \( m(1-q) \) are the rate at which people that exposed to non-resistant virus become recovered and infectious respectively, \( \mu \) is the rate at which infectious to oseltamivir resistant virus become recovered by taking nalidixic acid or dorzolomide drugs, \( \gamma \) is the rate at which infectious to non-resistant virus become recovered by taking oseltamivir drug. It follows that:

\[ \frac{dN}{dt} = (S + E_R + I_R + E_U + I_U + R) = \Lambda - dS \]

Therefore the possible region for (1) is:

\[ \Omega = \left\{ (S, E_R, I_R, E_U, I_U, R) : S > 0, E_R \geq 0, I_R \geq 0, E_U \geq 0, I_U \geq 0, S + E_R + I_R + E_U + I_U + R \leq \frac{\Lambda}{d} \right\} \]

It is obvious that \( \Omega \) is positively invariant with respect to (1).

2.2. Equilibria

Setting the equations in (1) equal to zero, and solving simultaneously we get three equilibrium points:

i) Disease free equilibrium,

\[ E_0 = \left( \frac{\Lambda}{d}, 0, 0, 0, 0 \right) \]
ii) non-resistance virus free equilibrium,

$$E_1 = \left( \frac{\mu}{\alpha(1-p)}, \frac{\alpha\lambda - \alpha\lambda\rho - \mu d}{\alpha k(1-p)}, \frac{\alpha\lambda - \alpha\lambda\rho - \mu d}{\alpha\mu}, 0, 0 \right)$$

iii) Oseltamivir - resistance virus free equilibrium,

$$E_2 = \left( \frac{\gamma}{\beta(1-q)}, 0, 0, \frac{\beta\lambda - \beta\lambda q - \gamma d}{\beta m(1-q)}, \frac{\beta\lambda - \beta\lambda q - \gamma d}{\beta\gamma} \right)$$

2.3. Basic Reproduction Ratio

Basic reproduction ratio (R0) is the number of secondary infections caused by one infectious individual in a wholly susceptible population. We use the next Generation matrix as used in\textsuperscript{13} to determine the R0.

$$F = \begin{bmatrix} kE_R & 0 & 0 & 0 & 0 \\ \mu E_R - k(1-p) E_R & 0 & 0 & 0 & 0 \\ 0 & 0 & m E_U & 0 & 0 \\ 0 & 0 & 0 & 0 & -m(1-q) \gamma \end{bmatrix} FV^{-1} = \begin{bmatrix} \frac{\alpha S(1-p)}{\mu} & \frac{\alpha S}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta S(1-q)}{\gamma} & \frac{\beta S}{\gamma} \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

The eigenvalues are

$$\lambda_1 = \lambda_2 = 0 \quad \lambda_3 = \frac{\alpha S(1-p)}{\mu}, \quad \lambda_4 = \frac{\beta S(1-q)}{\gamma}$$

Therefore, the spectral radius R(FV\textsuperscript{-1}) is \(\frac{\alpha S(1-p)}{\mu}\) and \(\frac{\beta S(1-q)}{\gamma}\).

Hence we have, \(R_0^1 = \frac{\alpha S(1-p)}{\mu}\), \(R_0^2 = \frac{\beta S(1-q)}{\gamma}\).

3. Local and Global Stability of DFE

In this chapter local and global stability of the disease free equilibrium are found.

3.1. Local Stability of the Disease Free Equilibrium

Theorem 1: \(E_0\) is locally asymptotically stable if \(R_0^1 \leq 1\) and \(R_0^2 \leq 1\), unstable otherwise.

Proof: Jacobian matrix at \(E_0\) is given as,

$$J(E_0) = \begin{bmatrix} -d & 0 & -\alpha S & 0 & -\beta S^* \\ 0 & -k & \alpha S^* & 0 & 0 \\ 0 & k(1-p) & -\mu & 0 & 0 \\ 0 & 0 & 0 & -m & \beta S^* \\ 0 & 0 & 0 & m(1-q) & -\gamma \end{bmatrix}$$

Eigenvalues of \(J\left(E_0\right)\) are
\[ \lambda_1 = -d, \lambda_2 = -\gamma \]

\[ \lambda_3 = -\frac{1}{2} k - \frac{1}{2} \mu + \frac{1}{2} \sqrt{-4 S a k p + 4 S a k + k^2 - 2 \mu k + \mu^2} \]
\[ \lambda_4 = -\frac{1}{2} k - \frac{1}{2} \mu - \frac{1}{2} \sqrt{-4 S a k p + 4 S a k + k^2 - 2 \mu k + \mu^2} \]

\[ \lambda_5 = -\frac{1}{2} m - \frac{1}{2} \gamma + \frac{1}{2} \sqrt{-4 S \beta m q + 4 S \beta m + \gamma^2 - 2 \gamma m + m^2} \]
\[ \lambda_6 = -\frac{1}{2} m - \frac{1}{2} \gamma - \frac{1}{2} \sqrt{-4 S \beta m q + 4 S \beta m + \gamma^2 - 2 \gamma m + m^2} \]

Taking

\[ \lambda_3 = -\frac{1}{2} k - \frac{1}{2} \mu + \frac{1}{2} \sqrt{-4 S a k p + 4 S a k + k^2 - 2 \mu k + \mu^2} = \frac{1}{2} \left[ -(k + \mu) + \sqrt{(\mu + k)^2 - 4 \mu k \left(1 - R_0^1\right)} \right] < 0 \]

If,

\[ (\mu + k)^2 - 4 \mu k \left(1 - R_0^1\right) < (\mu + k)^2 \Rightarrow \mu k \left(1 - R_0^1\right) > 0 \Rightarrow R_0^1 < 1 \]

\[ \lambda_4 = -\frac{1}{2} k - \frac{1}{2} \mu - \frac{1}{2} \sqrt{-4 S a k p + 4 S a k + k^2 - 2 \mu k + \mu^2} = -\frac{1}{2} \left[ (\mu + k) + \sqrt{(\mu + k)^2 - 4 \mu k \left(1 - R_0^1\right)} \right] \]

To show that

\[ \sqrt{(\mu + k)^2 - 4 \mu k \left(1 - R_0^1\right)} \] is not complex it is enough to show that \((\mu + k)^2 - 4 \mu k \left(1 - R_0^1\right) > 0\),

\[ (\mu + k)^2 - 4 \mu k \left(1 - R_0^1\right) = (\mu - k)^2 4 \mu k R_0^1 > 0, \text{ since } (\mu - k)^2 > 0 \]

Similarly, \(\lambda_4\) and \(\lambda_6\) can be shown to be negative by following the same procedure if \(R_0^2 \leq 1\).

### 3.2. Global Stability of the Disease Free Equilibrium

**Theorem 2:** If \(R_0^1 \leq 1\) and \(R_0^2 \leq 1\), then the DFE \(E_0\) is globally asymptotically stable in \(\Omega\).

**Proof:** We construct the following Lyapunov function

\[ V(t) = k I_R + k(1 - p)E_R + \mu I_U + m(1 - q)E_U > 0 \]

\[ \dot{V} = k \dot{I}_R + k(1 - p) \dot{E}_R + \mu \dot{I}_U + m(1 - q) \dot{E}_U \]
\[ = k \left[ k(1 - p)E_R - \mu I_R \right] + k(1 - p) \left[ \alpha SI_R - kE_R \right] + m \left[ m(1 - q)E_U - \gamma I_U \right] + m(1 - q) \left[ \beta SI_U - mE_U \right] \]
\[ = k \left[ -\mu + (1 - p)\alpha S \right] + m \left[ -\gamma + (1 - q)\beta S \right] = -k \mu \left( 1 - p \right) \alpha S - m \left( 1 - q \right) \beta S \]
\[ < 0 \]

If \(R_0^1, R_0^2 < 1\).

\[ \dot{V} = 0 \text{ iff } S = N, E_R = E_U = I_R = I_U = 0. \text{ Hence by Lasalle invariance principle } E_0 \text{ is globally asymptotically stable} \]

in \(\Omega\) when \(R_0^1, R_0^2 \leq 1\).
4. Local and Global Stability of Endemic Equilibria

In this chapter local and global stability of the endemic equilibria are found.

4.1. Local and Global Stability of $E_1$

Theorem 3: The endemic equilibrium $E_1$ is locally asymptotically stable in $\Omega$ for $R_0^1 > 1$.

Proof

$$E_1 = \left( \frac{\mu}{\alpha(1-p)}, \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha k(1-p)}, \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha \mu}, 0, 0 \right)$$

$$S_1 = \frac{S_0}{\alpha (1-p)}S_0 = \frac{S_0}{R_0} > 0$$

$$E_{R_1} = \frac{\alpha\Lambda p - \alpha\Lambda + d\mu}{-\alpha k(1-p)} = \frac{\Lambda}{k} - \frac{dS^*}{k} \frac{1}{\alpha(1-p)S^*} = \frac{\Lambda}{k} - \frac{dS^*}{k} \frac{1}{R_0^1}$$

$$E_{R_1} = \frac{\alpha\Lambda p - \alpha\Lambda + d\mu}{-\alpha k(1-p)} = \frac{\Lambda}{k} - \frac{d}{k} \frac{1}{R_0^1} = \frac{\Lambda}{k} \left( \frac{1}{R_0^1} - 1 \right) > 0$$

If $R_0^1 > 1$

$$I_{R_1} = \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha \mu} = \frac{\Lambda}{\alpha S^*} \frac{\alpha S^* (1-p)}{\mu} - \frac{d}{\alpha} = \frac{\Lambda}{\alpha S^*} R_0^1 - \frac{d}{\alpha} = \frac{d}{\alpha} \left( R_0^1 - 1 \right) > 0$$

If $R_0^1 > 1$.

Theorem 4: If $R_0^1 > 1$, then the endemic equilibrium $E_1$ is globally asymptotically stable.

Proof: We define a Lyapunov function $V$ as follows:

$$V = \left( S - S^* - \ln \frac{S}{S^*} \right) + \left( E_R - E^*_R - \ln \frac{E_R}{E^*_R} \right) + \left( I_R - I^*_R - \ln \frac{I_R}{I^*_R} \right)$$

$$V = S \left( 1 - \frac{S^*}{S} \right) + E_R \left( 1 - \frac{E^*_R}{E_R} \right) + I_R \left( 1 - \frac{I^*_R}{I_R} \right)$$

Consider,

$$S \left( 1 - \frac{S^*}{S} \right) = (\Lambda - \alpha SI_R - \beta SI_U - dS) \left( 1 - \frac{S^*}{S} \right)$$

Since,

$$\Lambda = \alpha S^* I_R + \beta S^* I_U + dS^*$$

and

$$S^* = \frac{\mu}{\alpha(1-p)}$$
\[
S \left( 1 - \frac{S}{S} \right) = (\alpha S I_R + \beta S U + \alpha S I + \alpha S L - \alpha S - \beta S U - dS \left( 1 - \frac{\mu}{\alpha (1-p)} S \right) \left( 1 - \frac{1}{R_0^1} \right) \\
= \left[ \alpha \left( S I_R - \frac{\mu}{\alpha (1-p)} \right) + \beta \left( S U - 0 \right) - d \left( S - \frac{\mu}{\alpha (1-p)} \right) \left( 1 - \frac{1}{R_0^1} \right) \right] \\
= \left[ \alpha S I_R + \beta S U + d \left( S - S_r \right) \left( 1 - \frac{1}{R_0^1} \right) \right] < 0
\]

If \( R_0^1 > 1 \).

\[
\dot{E}_R \left( 1 - \frac{E_{R_1}}{E_R} \right) = \left( \alpha S I_R - k E_R \right) \left( 1 - \frac{E_{R_1}}{E_R} \right) = \alpha S I_R - k E_R - \frac{I_R}{E_R} \alpha S E_{R_1} + k E_R
\]

\[
= \alpha S I_R - k E_R - \frac{I_R}{E_R} \left( \alpha S \frac{\alpha S_0}{\alpha (1-p)} - \frac{\mu d}{\alpha (1-p)} \right) + k \left( \alpha S \frac{\mu d}{\alpha (1-p)} - \frac{\mu d}{\alpha (1-p)} \right) = \alpha S I_R - k E_R - \frac{\alpha (1-p)}{\alpha (1-p)} \left( 1 - \frac{1}{R_0^1} \right)
\]

If

\[
1 < \frac{\Lambda}{k E_R} \left( 1 - \frac{1}{R_0^1} \right) \Rightarrow R_0^1 > \frac{1}{1 - k E_R} > 1
\]

Lastly,

\[
I_R \left( 1 - \frac{I_{R_1}}{I_R} \right) = \left( k (1-p) E_R - \mu I_R \right) \left( 1 - \frac{I_{R_1}}{I_R} \right) = k (1-p) E_R - \mu I_R - \frac{I_R}{E_R} \mu I_R - \frac{E_R}{I_R} (1-p) I_{R_1} + \mu I_{R_1}
\]

\[
= k (1-p) E_R - \mu I_R - \frac{E_R}{I_R} \left( \frac{\alpha S_0}{\mu} \right) \frac{\alpha S_0}{\mu} \left( 1 - p \right) + \frac{E_R}{I_R} \left( 1 - p \right) \left( 1 - p \right) + \mu d \left( R_0^1 - 1 \right)
\]

If

\[
1 < \frac{\Lambda}{k E_R} \left( R_0^1 - 1 \right) \Rightarrow R_0^1 > 1 + \frac{\alpha I_R}{d} > 1 \text{ since } \frac{\alpha I_R}{d} > 0
\]

This implies if \( R_0^1 > 1 \) then \( E_R \) is globally asymptotically stable.
4.2. Local and Global Stability of $E_2$

Theorem 5: The endemic equilibrium $E_2$ is locally asymptotically stable in $\Omega$ for $R_0^2 > 1$.

Proof

$$E_2 = \left( \frac{\gamma}{\beta(1-q)}, 0, 0, \frac{\beta \Lambda - \beta \Lambda q - \gamma d}{\beta m(1-q)}, \frac{\beta \Lambda - \beta \Lambda q - \gamma d}{\beta \gamma} \right)$$

$$S_2 = \frac{\gamma}{\beta(1-q)} = \frac{S^*}{\beta S^*(1-q)} = \frac{S^*}{R_0^2}$$

$$E_{U2} = \frac{\beta \Lambda - \beta \Lambda q - \gamma d}{\beta m(1-q)} = \frac{\beta \Lambda (1-q)}{\beta m(1-q)} - \frac{\gamma d}{\beta m(1-q)} = \frac{\Lambda - d}{m - m R_0^2}$$

Since, $S^* = \frac{\Lambda}{d}$ then, $E_{U2} = \frac{\Lambda}{m} \left( 1 - \frac{1}{R_0^2} \right) > 0$ if $R_0^2 > 1$.

$$I_{U2} = \frac{\beta \Lambda - \beta \Lambda q - \gamma d}{\beta \gamma} = \frac{\beta \Lambda (1-q)}{\beta \gamma} - \frac{\gamma d}{\beta \gamma} = \frac{\Lambda}{\beta} \left( \frac{\beta S^*(1-q)}{\gamma} - \frac{d}{\beta} \left( R_0^2 - 1 \right) > 0 \right)$$

If $R_0^2 > 1$

Theorem 6: If $R_0^2 > 1$ , then the endemic equilibrium $E_2$ is globally asymptotically stable.

Proof: The proof is similar to the global stability of $E_1$ , with $R_0^1 > 1$ replaced by $R_0^2 > 1$.

5. Conclusions

In this paper, a proposed model for influenza virus with both resistance and non - resistance to Oseltamivir is introduced. The Basic Reproduction Ratios $R_0^1$ and $R_0^2$ that determines the propagation dynamics of the disease is determined. When $R_0^1 \leq 1$ and $R_0^2 \leq 1$ the system has only a disease free equilibrium $E_0$ which is globally asymptotically stable. When $R_0^1 > 1$ and $R_0^2 > 1$ then the system has endemic equilibria $E_1$ and $E_2$ which are globally asymptotically stable. Global stabilities were determined using Lyapunov functions.

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