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Modelling the impact of vaccination on infectious diseases dynamics

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This paper investigates consequences of vaccine implementation strategies for infectious diseases by a mathematical model. For an infectious disease, the degree of infection may vary widely among the individuals. Reports show that individuals belonging to certain groups possess considerably higher risk to infection. Incorporating this phenomenon into vaccination strategies, the host is categorized into different groups to measure the outcome of the vaccination. A mathematical model is proposed and analysed to evaluate this measure. Our results suggest that vaccinating a group with certain priority may lead to elimination of the disease effectively. The strategy is cost-effective as well.

Keywords: HIV; vaccination; basic reproduction number; global attractivity; Lyapunov function

AMS Subject Classification: 34K18; 34K20; 92D30

1. Introduction

Vaccine has had a successful history since Edward Jenner's discovery of smallpox vaccine in the eighteenth century [18]. His innovation is widely regarded as the foundation of immunology. With the rapid pace of vaccine development medical science has saved millions of lives from dreadful diseases during the last two centuries. Small pox eradication can be worth mentioning as a successful example in this regard [1, 30]. Vaccines also contribute significantly to reducing infections of influenza, polio and many other life threatening diseases [21, 29]. In today's life, it is unusual and rare for a child not to receive any vaccines.

A vaccine typically contains an agent that resembles a disease-causing microorganism which stimulates the immune system of host and builds up antibody against the virus to recognize the agent as a foreigner. Thus, whenever such a microorganism is encountered within a host, the immune system destroys it. This kind of phenomenon is known as immunity. Thus, as long as a vaccine for a disease is available, it is an ideal means of protecting a healthy population from the disease.

An individual may receive vaccines available for a disease that is prevalent in his region. Vaccines of some diseases are already developed and one can take the vaccine if the particular

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disease is threat for him. For example, an individual can take a polio vaccine or a seasonal flu vaccine which are already available. However, when a new infectious disease emerges but no vaccine is available for it, the disease may cause significant infections and deaths. It takes some time to devise an effective vaccine if successful.

Once a vaccine is available, a natural and immediate question arises: how to allocate and implement this vaccine [31, 34]. Certainly we cannot vaccinate all the individuals to eradicate the disease overnight. In addition to social and ethical issues, high cost may prevent universal distribution of vaccines [25]. Certain group of individuals may pose higher risk to the infections than the others. In influenza, for example, school-going children can be infected more easily and can spread the disease more rapidly than other individuals [10, 16, 20, 21]. Thus to control infections by using vaccines, a proper distribution and implementation strategy is very important. Priority may need to be given to certain group(s) or individuals by the health professionals. Current practice of vaccine allocation highlights the importance of identifying the groups which are at highest risk for adverse health [24]. Effectiveness of such a vaccine allocation strategy can be determined through analysis of a mathematical model. In this paper, we aim to shed some light on this critical issue and hope to provide a useful guideline to the policy-maker.

To properly implement the vaccination campaign, a plausible and intellectual idea may be to immunize individuals belonging to certain groups or locations that are most vulnerable to infections. The transmission rates in these groups are much higher than those in the other groups in which individuals are less susceptible or they are located in a comparatively safe area. The individuals in the target groups may need more protections so that the overall infections can be controlled effectively. In this paper, we formulate and analyse a mathematical model that incorporates prioritized group-vaccination strategy.

The rest of this paper is organized as follows. In Section 2, we formulate a two-group model based on the individual's risk status. The basic reproduction number of the model, the equilibria of the model and their stability, as well as the disease persistence are discussed in Section 3. Finally, in Section 4, we discuss the policy of vaccine allocation and distribution based on the model outcomes and offer some concluding remarks.

2. Mathematical model

As indicated in the previous section, we divide the total population into two groups: the risky (r) group in which the infection rates are much higher within the group; and the critical (c) group in which the individuals are conscious in their social behaviour, or the individuals that remain isolated and are less likely to have contact with the infected group, and subsequently their infection rate is much lower within the group.

Let the number of population in each group be divided into susceptible (S) and infected (I) sub-classes. Having infection from either infected sub-class, a susceptible individual becomes infected and remains in that sub-class in his/her entire life. The susceptible individuals from each group are vaccinated at a constant rate and transferred into a common vaccinated (V) sub-class. We do not consider the vertical infection and assume that susceptibles are recruited at constant rates. The flow diagram of population is shown in Figure 1.

As mentioned earlier, we consider two different groups in the population according to their risk level. The symbols and notations are explained in Table 1. The infection mechanism is considered to be followed by saturating incidence [2, 3, 15] defined by

$$h(I) = \frac{I}{1 + \alpha I}, \tag{1}$$

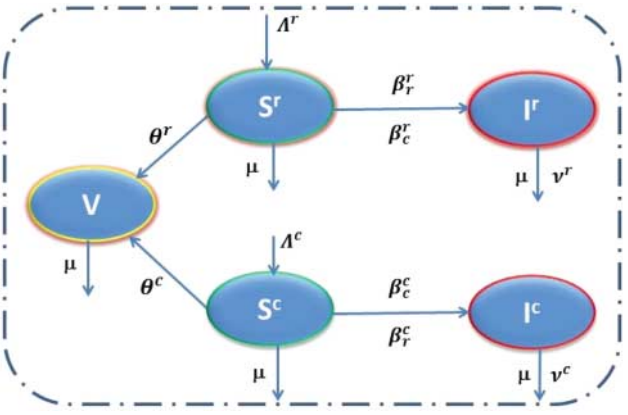

Figure 1. Schematic diagram.

Table 1. Description of variables and parameters of model (3).

Parameter	Description
S^r	Number of susceptible in group r
S^c	Number of susceptible in group c
I^r	Number of infected in group r
I^P	Number of infected in group c
V	Number of vaccinated individuals
N	Total number of individuals
β_i^j	Contact rate of susceptible and infective $(i, j = r, c)$
ν^i	Disease-induced death rate $(i = r, c)$
μ	Natural death rate
θ^r	Vaccination rate to the group r
θ^c	Vaccination rate to the group c

where $\alpha \geq 0$ determines the saturation level when the infectious population is large. When $\alpha = 0$, this reduces to the mass action incidence rate. The infection rate increases with the number of infected individuals when this number is small. As the infected number increases the infection rate becomes plateaued. This phenomenon reflects the saturation of infected numbers also known as 'crowding effect'. With this assumption the dynamics of the population is governed by the following equations:

$$\begin{aligned}
\dot{S}^r &= \Lambda^r - \left(\beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \theta^r) S^r, \\
\dot{S}^c &= \Lambda^c - \left(\beta_r^c \frac{I^r}{1+\alpha_r I^r} + \beta_c^c \frac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \theta^c) S^c, \\
\dot{I}^r &= \left(\beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \nu^r) I^r, \\
\dot{I}^c &= \left(\beta_r^c \frac{I^r}{1+\alpha_r I^r} + \beta_c^c \frac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \nu^c) I^c, \\
\dot{V} &= \theta^r S^r + \theta^c S^c - \mu V.
\end{aligned} \tag{2}$$

We distinguish the groups according to contact rates and our assumption is

$$\beta_r^r \gg \beta_r^c \geq \beta_c^r \gg \beta_c^c.$$

3. Analysis of the model

3.1. *Well-posedness of the model*

The model (2) consists of five equations, but the last equation is decoupled. To analyse the model, it suffices to consider the dynamics of the following system:

$$\begin{aligned}
\dot{S}^r &= \Lambda^r - \left(\beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \theta^r) S^r, \\
\dot{S}^c &= \Lambda^c - \left(\beta_r^c \frac{I^r}{1+\alpha_r I^r} + \beta_c^c \frac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \theta^c) S^c, \\
\dot{I}^r &= \left(\beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \nu^r) I^r, \\
\dot{I}^c &= \left(\beta_r^c \frac{I^r}{1+\alpha_r I^r} + \beta_c^c \frac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \nu^c) I^c.
\end{aligned} \tag{3}$$

For biological reason, we need to investigate the boundedness and positivity of the solutions of our model. To this end, the first equation can be written as

$$\dot{S}^r = \Lambda^r - \phi(t) S^r,$$

where

$$\phi(t) = \beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c} + \mu + \theta^r.$$

It follows that

$$S^r = S_0^r \, \mathrm{e}^{-\int_0^t \phi(s)\,\mathrm{d}s} + \Lambda^r \, \mathrm{e}^{-\int_0^t \phi(s)\,\mathrm{d}s} \int_0^t \mathrm{e}^{\int_0^\tau \phi(s)\,\mathrm{d}s}\,\mathrm{d}\tau,$$

which is non-negative as long as $S_0^r \geq 0$. Similarly, it can be shown that $S^c \geq 0$. To show that I^r and I^c are non-negative, consider the sub-system of Equation (3)

$$\begin{aligned}
\dot{I}^r &= \left(\beta_r^r \frac{I^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c}{1+\alpha_c I^c}\right) S^r - (\mu + \nu^r) I^r, \\
\dot{I}^c &= \left(\beta_r^c \frac{I^r}{1+\alpha_r I^r} + \beta_c^c \frac{I^c}{1+\alpha_c I^c}\right) S^c - (\mu + \nu^c) I^c.
\end{aligned} \tag{4}$$

Since S^r and S^c are non-negative, this sub-system is cooperative. By monotone property [32], we conclude that I^r and I^c are non-negative provided that $I^r(0) \geq 0$ & $I^c(0) \geq 0$.

Now, we consider the boundedness of the model. By adding all the equations in (3), it can be shown that the total number of individuals satisfies

$$\lim_{t\to\infty} \sup(S^r + S^c + I^r + I^c) \leq \frac{(\Lambda^r + \Lambda^c)}{(\mu + \theta)},$$

where $\theta = \min\{\theta^r, \theta^c\}$. Therefore, the biologically feasible region of the model (3) is

$$\Omega = \left\{(S^r, S^c, I^r, I^c) : S^r, S^c, I^r, I^c \geq 0, S^r + S^c + I^r + I^c \leq \frac{(\Lambda^r + \Lambda^c)}{(\mu + \theta)}\right\}.$$

3.2. *Basic reproduction number*

The model (3) has a disease-free equilibrium (DFE) $E_0(\Lambda^r/(\mu+\theta^r), \Lambda^c/(\mu+\theta^c), 0, 0)$, but there is no boundary equilibria (i.e. one infected class is present while other is absent). The stability of E_0 is closely related to the notion of the basic reproduction number for the model, denoted by $\mathfrak{R}_o$, which plays an important role in determining the disease persistence. The number $\mathfrak{R}_o$ is defined as 'the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual' (see, e.g. [7]). This threshold parameter determines whether the disease persists or dies out from the population. We use next-generation matrix [8] to compute $\mathfrak{R}_o$. The non-negative matrix F and the non-singular M-matrix V, known as new-infection and transition matrices respectively, for the system (3), are given by

$$F = \begin{pmatrix} \beta_r^r \dfrac{\Lambda^r}{(\mu+\theta^r)} & \beta_c^r \dfrac{\Lambda^r}{(\mu+\theta^r)} \\ \beta_r^c \dfrac{\Lambda^c}{(\mu+\theta^c)} & \beta_c^c \dfrac{\Lambda^c}{(\mu+\theta^c)} \end{pmatrix}, \quad V = \begin{pmatrix} \mu+\nu^r & 0 \\ 0 & \mu+\nu^c \end{pmatrix}.$$

It follows that

$$FV^{-1} = \begin{pmatrix} \beta_r^r \dfrac{\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)} & \beta_c^r \dfrac{\Lambda^r}{(\mu+\theta^r)(\mu+\nu^c)} \\ \beta_r^c \dfrac{\Lambda^c}{(\mu+\theta^c)(\mu+\nu^r)} & \beta_c^c \dfrac{\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)} \end{pmatrix}.$$

The basic reproduction number is then defined by

$$\mathfrak{R}_o = \rho(FV^{-1}).$$

By Theorem 2 in [8], we obtain the following result on the stability/instability of E_0.

THEOREM 3.1 *If $\mathfrak{R}_o < 1$, the DFE E_0 is locally asymptotically stable; it becomes unstable if $\mathfrak{R}_o > 1$.*

3.3. *Global stability of E_0*

In this section, we study the global stability of the DFE E_0 for the model (3). The *local* stability of E_0 is already established by Theorem 3.1; however, we use this theorem to further obtain the *global* stability of E_0.

The Jacobian matrix of Equation (3) at E_0 is given by

$$J(E_0) = \begin{pmatrix} -(\mu+\theta^r) & 0 & -\beta_r^r \dfrac{S_0^r}{N_0} & -\beta_c^r \dfrac{S_0^r}{N_0} \\ 0 & -(\mu+\theta^c) & -\beta_r^c \dfrac{S_0^c}{N_0} & -\beta_c^c \dfrac{S_0^c}{N_0} \\ 0 & 0 & \beta_r^r \dfrac{S_0^r}{N_0} - (\mu+\nu^r) & \beta_c^r \dfrac{S_0^r}{N_0} \\ 0 & 0 & \beta_r^c \dfrac{S_0^c}{N_0} & \beta_c^c \dfrac{S_0^c}{N_0} - (\mu+\nu^c) \end{pmatrix}.$$

Clearly, $-(\mu+\theta^r)$ and $-(\mu+\theta^c)$ are two eigenvalues of $J(E_0)$ which are negative, and the other two eigenvalues are determined by the lower right block of $J(E_0)$, that is,

$$J_{22}=\begin{pmatrix}\beta_r^r\dfrac{\Lambda^r}{(\mu+\theta^r)}-(\mu+\nu^r) & \beta_c^r\dfrac{\Lambda^r}{(\mu+\theta^r)}\\ \beta_r^c\dfrac{\Lambda^c}{(\mu+\theta^c)} & \beta_c^c\dfrac{\Lambda^c}{(\mu+\theta^c)}-(\mu+\nu^c)\end{pmatrix}.$$

Hence, the stability of E_0 fully depends on the matrix J_{22}.

For any given square matrix A, let $s(A)$ denote the stability modulu of A (i.e. the largest real part of all eigenvalues of A). Combining the above observation and with Theorem 3.1, we immediately have following corollary.

COROLLARY 3.2 *If $\Re_o<1$, then $s(J_{22})<0$; if $\Re_o>1$, then $s(J_{22})>0$.*

We are now able to prove the following *global* result.

THEOREM 3.3 *When $\Re_0<1$, E_0 is indeed globally asymptotically stable.*

Proof From the $\dot{S}^r$ equation in (3), we have $\dot{S}^r\le\Lambda^r-(\mu+\theta^r)S^r$, which implies that

$$\limsup_{t\to\infty}S^r(t)\le\frac{\Lambda^r}{\mu+\theta^r}.$$

Similarly,

$$\limsup_{t\to\infty}S^c(t)\le\frac{\Lambda^c}{\mu+\theta^c}.$$

Thus, for any $\varepsilon>0$, there exists $T_1>0$ such that

$$S^r(t)\le\frac{\Lambda^r+\varepsilon}{(\mu+\theta^r)},\quad S^c(t)\le\frac{\Lambda^c+\varepsilon}{(\mu+\theta^c)}\ \text{ for } t\ge T_1. \tag{5}$$

Applying the estimates in Equations (5) to (4), we obtain

$$\begin{aligned}\begin{pmatrix}\dot{I}^r\\ \dot{I}^c\end{pmatrix}&=\begin{pmatrix}\left(\beta_r^r\dfrac{I^r}{1+\alpha_rI^r}+\beta_c^r\dfrac{I^c}{1+\alpha_cI^c}\right)S^r-(\mu+\nu^r)I^r\\ \left(\beta_r^c\dfrac{I^r}{1+\alpha_rI^r}+\beta_c^c\dfrac{I^c}{1+\alpha_cI^c}\right)S^c-(\mu+\nu^c)I^c\end{pmatrix}\\ &\le\begin{pmatrix}(\beta_r^rI^r+\beta_c^rI^c)S^r-(\mu+\nu^r)I^r\\ (\beta_r^cI^r+\beta_c^cI^c)S^c-(\mu+\nu^c)I^c\end{pmatrix}\\ &\le\begin{pmatrix}\beta_r^r\dfrac{\Lambda^r+\varepsilon}{(\mu+\theta^r)}-(\mu+\nu^r) & \beta_c^r\dfrac{\Lambda^r}{(\mu+\theta^r)}\\ \beta_r^c\dfrac{\Lambda^c+\varepsilon}{(\mu+\theta^c)} & \beta_c^c\dfrac{\Lambda^c}{(\mu+\theta^c)}-(\mu+\nu^c)\end{pmatrix}\begin{pmatrix}I^r\\ I^c\end{pmatrix}\quad\text{for } t\ge T_1.\end{aligned}$$

Thus, the sub-system (4) has an upper comparison system which is linear and cooperative with following coefficient matrix:

$$A(\varepsilon)=\begin{pmatrix}\beta_r^r\dfrac{\Lambda^r+\varepsilon}{(\mu+\theta^r)}-(\mu+\nu^r) & \beta_c^r\dfrac{\Lambda^r+\varepsilon}{(\mu+\theta^r)}\\ \beta_r^c\dfrac{\Lambda^c+\varepsilon}{(\mu+\theta^c)} & \beta_c^c\dfrac{\Lambda^c+\varepsilon}{(\mu+\theta^c)}-(\mu+\nu^c)\end{pmatrix}.$$

Obviously, $A(\varepsilon)$ depends on ε continuously and $A(0) = J_{22}$. Since $s(J_{22}) < 0$, by continuity, we can choose ε sufficiently small so that $s(A(\varepsilon)) < 0$. Thus, all solutions of this comparing linear system tend to $(0, 0)^{\mathrm{T}}$ as $\to \infty$. By the standard comparison argument, we conclude that for every non-negative solution of Equation (3), its I^r and I^c components also approach to 0 as $t \to \infty$.

The above established limits $I^r(t) \to 0$ and $I^c(t) \to 0$ as $t \to \infty$ indicate that the sub-system of Equation (3) consisting of $\dot{S}^r$ and $\dot{S}^c$ equations has the following limit system:

$$\begin{aligned} \dot{S^r} &= \Lambda^r - (\mu + \theta^r)S^r, \\ \dot{S^c} &= \Lambda^c - (\mu + \theta^c)S^c. \end{aligned} \tag{6}$$

Since every solution of Equation (6) tends to $(\Lambda^r/(\mu + \theta^r), \Lambda^c/(\mu + \theta^c))^{\mathrm{T}}$, by the theory of asymptotically autonomous systems (see,e.g. Castillo-Chaves and Thieme [6]), the $(S^r(t), S^c(t))$ portion of any non-negative solution of Equation (3) also approaches $(\Lambda^r/(\mu + \theta^r), \Lambda^c/(\mu + \theta^c))^{\mathrm{T}}$. Therefore, every non-negative solution of Equation (3) converges to the DFE E_0. The global attractiveness of E^0 and the local stability established in Theorem 3.1 lead to the global asymptotical stability of E_0, completing the proof of the theorem. ■

3.4. *Persistence of the disease*

When $\mathfrak{R}_0 > 1$, the DFE becomes unstable and it is natural to expect that the infectious populations I^r and I^c will remain persistent in this case. In this subsection, we confirm this expectation. Indeed, we will prove the following theorem.

THEOREM 3.4 *Assume that $\mathfrak{R}_0 > 1$. Then, the disease is uniformly persistent in the sense that there exists an $\eta > 0$ such that for every positive solution of Equation* (3)*, there holds*

$$\liminf_{t\to\infty} I^r(t) > \eta, \quad \liminf_{t\to\infty} I^c(t) > \eta.$$

Moreover, there exists an endemic equilibrium in this case.

Proof We shall apply a theorem in [33] to prove the uniform persistence. To this end, we set

$$\begin{aligned} X &= \{(S^r, S^c, I^r, I^c) \in \mathbb{R}^4_+ : S^r, S^c, I^r, I^c \geq 0\}, \\ X_0 &= \{(S^r, S^c, I^r, I^c) \in X : I^r, I^c > 0\}, \\ Y &= \frac{X}{X_0} = \{(S^r, S^c, 0, 0) \in X : S^r, S^c \geq 0, \text{ and } I^r = 0 \text{ or } I^c = 0\}. \end{aligned}$$

Now, we show that the system (3) is uniformly persistent with respect to (X_0, Y). Since Y contains only a single equilibrium E_0, we need to show that $W^s(E_0) \cap X_0 = \phi$, where $W^s(E_0)$ denotes the stable manifold of E_0. Suppose this is not true. Then, there is a $(S^r_0, S^c_0, I^r_0, I^c_0) \in X_0$ and the corresponding solution of Equation (3) with this initial point satisfies

$$\lim_{t\to\infty} (S^r(t), S^c(t), I^r(t), I^c(t)) \to \left(\frac{\Lambda^r}{(\mu + \theta^r)}, \frac{\Lambda^c}{(\mu + \theta^c)}, 0, 0\right).$$

Thus, for any $\xi > 0$, there is $T_2 > 0$ such that

$$\begin{aligned} &\frac{(\Lambda^r - \xi)}{(\mu + \theta^r)} \le S^r \le \frac{(\Lambda^r + \xi)}{(\mu + \theta^r)}, \\ &\frac{(\Lambda^c - \xi)}{(\mu + \theta^c)} \le S_c \le \frac{(\Lambda^c + \xi)}{(\mu + \theta^c)} \quad \text{for } t \ge T_2. \\ &0 \le I^r \le \xi, \quad 0 \le I^c \le \xi, \end{aligned} \tag{7}$$

It follows from Equations (3) and (7) that

$$\begin{aligned} \begin{pmatrix} \dot{I}^r \\ \dot{I}^c \end{pmatrix} &\ge \begin{pmatrix} \beta_r^r \dfrac{\Lambda^r - \xi}{\mu + \theta^r} \dfrac{1}{1 + \alpha_r \xi} - (\mu + \nu^r) & \beta_c^r \dfrac{\Lambda^r - \xi}{\mu + \theta^r} \dfrac{1}{1 + \alpha_c \xi} \\ \beta_r^c \dfrac{\Lambda^c - \xi}{\mu + \theta^c} \dfrac{1}{1 + \alpha_r \xi} & \beta_c^c \dfrac{\Lambda^c - \xi}{\mu + \theta^c} \dfrac{1}{1 + \alpha_c \xi} - (\mu + \nu^c) \end{pmatrix} \begin{pmatrix} I^r \\ I^c \end{pmatrix}, \\ &=: \tilde{J}(\xi) \begin{pmatrix} I^r \\ I^c \end{pmatrix}, \quad \text{for } t \ge T_2. \end{aligned}$$

This means that the sub-system (4) has a lower comparison system which is linear and cooperative with the coefficient matrix

$$\tilde{J}(\xi) = \begin{pmatrix} \beta_r^r \dfrac{\Lambda^r - \xi}{\mu + \theta^r} \dfrac{1}{1 + \alpha_r \xi} - (\mu + \nu^r) & \beta_c^r \dfrac{\Lambda^r - \xi}{\mu + \theta^r} \dfrac{1}{1 + \alpha_c \xi} \\ \beta_r^c \dfrac{\Lambda^c - \xi}{\mu + \theta^c} \dfrac{1}{1 + \alpha_r \xi} & \beta_c^c \dfrac{\Lambda^c - \xi}{\mu + \theta^c} \dfrac{1}{1 + \alpha_c \xi} - (\mu + \nu^c) \end{pmatrix}.$$

Note that $s(\tilde{J}(\xi))$ is continuous in ξ and $s(\tilde{J}(0)) > 0$ (since $\Re_0 > 1$), we can choose $\xi > 0$ sufficiently small such that $s(\tilde{J}(\xi)) > 0$, implying that positive solutions of the lower comparing system grow exponentially. By the standard comparison argument, $I^r(t)$ or/and $I^c(t)$ components of the solution of Equation (3) grow unbounded as $t \to \infty$. This is a contradiction to the fact that the solutions of the system (3) are ultimately bounded. Therefore, $W^s(E_0) \cap X_0 = \phi$. Now, the persistence of the system (3) follows from Theorem 4.6 in [33]. Furthermore, by Theorem 3.3 in [14], we know that uniform persistence and the dissipativity established in the previous subsection implies that system (3) has an endemic equilibrium (i.e. all components are positive). The proof of the theorem is completed. ■

The stability of E^* will be discussed in the next subsection.

3.5. *Global stability of E^**

In this subsection, we investigate the global stability of the endemic equilibrium E^* under the condition $\Re_0 > 1$. To this end, we apply a Lyapunov function similar to those recently used by Guo *et al.* [12], Korobeinikov and Maini [17] and McCluskey [22]. Such Lyapunov functions take advantages of the properties of the function

$$g(x) = x - 1 - \ln(x),$$

which is positive in $(0, \infty)$ except at $x = 1$, where it vanishes. For convenience of notations in constructing Lyapunov functions, we also make use of the following two functions:

$$f_i(x) = \frac{x}{1 + \alpha_i x}, \quad i = c, r.$$

Now, we establish following result.

THEOREM 3.5 *The endemic equilibrium E_* is globally attractive whenever it exists.*

Proof Consider the Lyapunov function

$$V = S_*^r g\left(\frac{S^r}{S_*^r}\right) + S_*^c g\left(\frac{S^c}{S_*^c}\right) + I_*^r g\left(\frac{I^r}{I_*^r}\right) + I_*^c g\left(\frac{I^c}{I_*^c}\right) + V_* g\left(\frac{V}{V_*}\right).$$

Obviously, V is non-negative in the positive cone Ω and attains zero at E_*. We need to show that $\dot{V}$ is negative definite. Differentiating V along the trajectories of Equation (2), we obtain

$$\begin{aligned}
\dot{V} &= \left(1 - \frac{S_*^r}{S^r}\right)\dot{S}^r + \left(1 - \frac{S_*^c}{S^c}\right)\dot{S}^c + \left(1 - \frac{I_*^r}{I^r}\right)\dot{I}^r + \left(1 - \frac{I_*^c}{I^c}\right)\dot{I}^c + \left(1 - \frac{V_*}{V}\right)\dot{V} \\
&= \left(1 - \frac{S_*^r}{S^r}\right)\left(\Lambda^r - \beta_r^r \frac{I^r S^r}{1+\alpha_r I^r} - \beta_c^r \frac{I^c S^r}{1+\alpha_c I^c} - (\mu+\theta^r)S^r\right) \\
&\quad + \left(1 - \frac{S_*^c}{S^c}\right)\left(\Lambda^c - \beta_r^c \frac{I^r S^c}{1+\alpha_r I^r} + \beta_c^c \frac{I^c S^c}{1+\alpha_c I^c} - (\mu+\theta^c)S^c\right) \\
&\quad + \left(1 - \frac{I_*^r}{I^r}\right)\left(\beta_r^r \frac{I^r S^r}{1+\alpha_r I^r} + \beta_c^r \frac{I^c S^r}{1+\alpha_c I^c} - (\mu+\nu^r)I^r\right) \\
&\quad + \left(1 - \frac{I_*^c}{I^c}\right)\left(\beta_r^c \frac{I^r S^c}{1+\alpha_r I^r} + \beta_c^c \frac{I^c S^c}{1+\alpha_c I^c} - (\mu+\nu^c)I^c\right) \\
&\quad + \left(1 - \frac{V_*}{V}\right)(\theta^r S^r + \theta^c S^c - \mu V).
\end{aligned}$$

Now, using the equilibrium equation at E_* and simplifying, we have

$$\begin{aligned}
\dot{V} &= \beta_r^r S_*^r f_r(I_*^r)\left[2 + \frac{f_r(I^r)}{f_r(I_*^r)} - \frac{I_*^r S^r f_r(I^r)}{I^r S_*^r f_r(I_*^r)} - \frac{S_*^r}{S^r} - \frac{I^r}{I_*^r}\right] \\
&\quad + \beta_c^r S_*^r f_c(I_*^c)\left[2 + \frac{f_c(I^c)}{f_c(I_*^c)} - \frac{I_*^r S^r f_c(I^c)}{I^r S_*^r f_c(I_*^c)} - \frac{S_*^r}{S^r} - \frac{I^c}{I_*^c}\right] \\
&\quad + \beta_r^c S_*^c f_r(I_*^r)\left[2 + \frac{f_r(I^r)}{f_r(I_*^r)} - \frac{I_*^c S^c f_r(I^r)}{I^c S_*^c f_r(I_*^r)} - \frac{S_*^c}{S^c} - \frac{I^c}{I_*^c}\right] \\
&\quad + \beta_c^c S_*^c f_c(I_*^c)\left[2 + \frac{f_c(I^c)}{f_c(I_*^c)} - \frac{I_*^c S^c f_c(I^c)}{I^c S_*^c f_c(I_*^c)} - \frac{S_*^c}{S^c} - \frac{I^c}{I_*^c}\right] \\
&\quad + \mu S_*^r\left(2 - \frac{S_*^r}{S^r} - \frac{S^r}{S_*^r}\right) + \mu S_*^c\left(2 - \frac{S_*^c}{S^c} - \frac{S^c}{S_*^c}\right) \\
&\quad + \theta^r S_*^r\left(3 - \frac{S_*^r}{S^r} - \frac{V}{V_*} - \frac{S^r V_*}{S_*^r V}\right) + \theta^c S_*^c\left(3 - \frac{S_*^c}{S^c} - \frac{V}{V_*} - \frac{S^c V_*}{S_*^c V}\right).
\end{aligned}$$

In the above expression, the last four terms are obviously non-positive. We only need to show that the terms in the square brackets are non-positive. Due to similarity, we only deal with one group of square brackets and show that it is non-positive. By using g function defined in Equation (7),

we proceed with the expression of first square bracket of the last equation as

$$\begin{aligned}
&2+\frac{f_r(I^r)}{f_r(I_*^r)}-\frac{I_*^r S^r f_r(I^r)}{I^r S_*^r f_r(I_*^r)}-\frac{S_*^r}{S^r}-\frac{I^r}{I_*^r}\\
&\quad=-g\left(\frac{S^r}{S_*^r}\right)-\ln\left(\frac{S_*^r}{S^r}\right)-g\left(\frac{I_*^r S^r f_r(I^r)}{I^r S_*^r f_r(I_*^r)}\right)-\ln\left(\frac{I_*^r S^r f_r(I^r)}{I^r S_*^r f_r(I_*^r)}\right)+\frac{f_r(I^r)}{f_r(I_*^r)}-\frac{I^r}{I_*^r}\\
&\quad\le-\ln\left(\frac{I_*^r f_r(I^r)}{I^r f_r(I_*^r)}\right)+\frac{f_r(I^r)}{f_r(I_*^r)}-\frac{I^r}{I_*^r}\\
&\quad=-\ln\left(\frac{1+\alpha_r I_*^r}{1+\alpha_r I^r}\right)+\frac{I^r}{I_*^r}\left(\frac{1+\alpha_r I_*^r}{1+\alpha_r I^r}\right)-\frac{I^r}{I_*^r}.
\end{aligned}$$

Now, we show that the above quantity is non-positive. Let

$$h(x)=-\ln\left(\frac{1+ax_0}{1+ax}\right)+\frac{x}{x_0}\frac{1+ax_0}{1+ax}-\frac{x}{x_0}.$$

Taking the derivative, we have

$$h'(x)=\frac{1}{(1+ax)^2x_0}[ax_0(1+ax)+1+ax_0-(1+ax)^2].$$

Note that $h'(x)$ only has a positive zero x_0. It is easy to see that $h(x)$ attains the maximum only at x_0, which is 0. Consequently, $\dot{V}\le 0$ with equality holding only at the equilibrium E_*. By Hale and Lunel [13], all positive solutions approach $\mathcal{M}$, the largest invariant subset of the set $\{\mathrm{d}V/\mathrm{d}t=0\}$. Since $\mathrm{d}V/\mathrm{d}t$ is zero only at E_*, $\mathcal{M}=\{E_*\}$ is a singleton set. Thus, the equilibrium E_* is globally attractive. ■

4. Discussion

In this paper, we aim to investigate the vaccine implementation policy of an infectious disease in a resource constrained environment. Transmission of a disease largely depends on the nature of infected individuals, locations, modes of transmission and infection-causing organisms. Certain group(s) of people may have high risk of receiving and transmitting infections whereas other individuals exhibit less susceptibility and infectivity. Therefore, the infection of disease significantly depends on individual's risk level. Considering this fact, we have proposed a simple two-group model incorporating vaccination rates. In our analysis, the model demonstrates a global threshold dynamics in terms of the combined parameter $\mathfrak{R}_\circ$ — the secondary infection rate referred to as the basic reproduction number, as described in Theorems 3.1, 3.3–3.5. More precisely, if $\mathfrak{R}_\circ<1$, then the disease will be eliminated over time; and $\mathfrak{R}_\circ>1$ the disease will remain endemic and infectious populations will approach to positive constant levels.

Obviously, from the viewpoint of controlling the disease, one would naturally like to reduce the basic reproduction number. Thus, it is worthwhile to investigate how we can reduce $\mathfrak{R}_\circ$

effectively by a proper implementation of vaccines. Calculating the spectral radius of the next-generation matrix FV^{-1} gives the following explicit formula for $\mathfrak{R}_o$:

$$\begin{aligned}\mathfrak{R}_o &= \frac{1}{2}\left[\frac{\beta_r^r\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)} + \frac{\beta_c^c\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}\right.\\ &\quad\left.+\sqrt{\left(\frac{\beta_r^r\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)} - \frac{\beta_c^c\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}\right)^2 + \frac{4\beta_c^r\beta_r^c\Lambda^r\Lambda^c}{(\mu+\theta^r)(\mu+\nu^r)(\mu+\theta^c)(\mu+\nu^c)}}\right]\\ &= \frac{1}{2}[\beta_r^rG_r^r + \beta_c^cG_c^c + \sqrt{(\beta_r^rG_r^r - \beta_c^cG_c^c)^2 + 4\beta_c^r\beta_r^cG_c^rG_r^c}],\end{aligned}$$

where

$$G_r^r = \frac{\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)}, \quad G_c^r = \frac{\Lambda^c}{(\mu+\theta^r)(\mu+\nu^c)},$$
$$G_r^c = \frac{\Lambda^r}{(\mu+\theta^c)(\mu+\nu^r)}, \quad G_c^c = \frac{\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}.$$

Based on the above formula, we have following observations on $\mathfrak{R}_o$.

Observation I: The two groups are weakly connected

In this case, the contact matrix is nearly reducible, that is, at least one of the cross-contact rates β_c^r or β_r^c is near 0. Then, the threshold parameter $\mathfrak{R}_o$ has the following approximation:

$$\mathfrak{R}_0 \approx \tfrac{1}{2}[\beta_r^rG_r^r + \beta_c^cG_c^c + |(\beta_r^rG_r^r - \beta_c^cG_c^c)|] = \max\{\beta_r^rG_r^r, \beta_c^cG_c^c\}.$$

Due to higher contact rate of risky group, we may assume that $\beta_r^rG_r^r > \beta_c^cG_c^c$. Then, we have

$$\mathfrak{R}_o \approx \beta_r^rG_r^r = \frac{\beta_r^r\Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)}.$$

That is, $\mathfrak{R}_o$ does not depend on vaccination of critical group anymore. Moreover, $\mathfrak{R}_o$ is decreasing with θ^r (the vaccination rate of risky group). The vaccination rate has positive effect on the reduction of disease. The condition $\beta_r^rG_r^r > \beta_c^cG_c^c$ will hold in a region where the disease is highly infectious (just like Ebola outbreak in West African countries [9, 19]). In this situation, when question arises on vaccine implementation, 'vaccine to risky group only' strategy would be better policy. This policy seems to be more crucial when vaccines are economically costly and insufficient, and more doses are required to provide full-immunity. Providing enough doses to the risky individuals rather than single shot to randomly chosen individuals from both groups should be more effective to control disease.

Now, we consider the case $\beta_r^rG_r^r < \beta_c^cG_c^c$ which may occur when the recruitment to risky group is significantly smaller than that in the critical group. This scenario prevails in a region where comparatively greater portion of the population are less susceptive (small β_c^c) and incoming susceptibles with lower susceptibility are also considerably larger (big Λ^c) in the respective group. By symmetry, the basic reproduction number becomes

$$\mathfrak{R}_o \approx \beta_c^cG_c^c = \frac{\beta_c^c\Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}.$$

It is surprising that vaccine to the risky individuals do not bring any benefit to reduce $\mathfrak{R}_o$. Because of weak connections ($\beta_c^r \approx 0$ or $\beta_r^c \approx 0$) between the groups, the risky group could not deteriorate the disease situation in the whole population. However, the susceptible individuals

in this group are more vulnerable to infection. So, if vaccines are available they also need to be immunized to protect them even though this vaccination may not have a major effect on global disease control.

Observation II: Both groups are strongly connected

Now, we investigate the scenario when both groups are strongly connected (i.e. contacts matrix is irreducible). Assume that both cross-contact rates β_c^r and β_r^c are positive. We need to look into the threshold parameter $\mathfrak{R}_o$ more deeply. Observe that $\mathfrak{R}_o$ depends on four compound parameters $\beta_r^r G_r^r$, $\beta_c^r G_c^r$, $\beta_r^c G_r^c$ and $\beta_c^c G_c^c$. So, we need to determine the key parameter among the following four components:

$$\beta_r^r G_r^r = \frac{\beta_r^r \Lambda^r}{(\mu+\theta^r)(\mu+\nu^r)}, \quad \beta_c^r G_c^r = \frac{\beta_c^r \Lambda^r}{(\mu+\theta^r)(\mu+\nu^c)},$$
$$\beta_r^c G_r^c = \frac{\beta_r^c \Lambda^c}{(\mu+\theta^c)(\mu+\nu^r)}, \quad \beta_c^c G_c^c = \frac{\beta_c^c \Lambda^c}{(\mu+\theta^c)(\mu+\nu^c)}$$

that contribute more to increase $\mathfrak{R}_o$ in the absence of vaccination. Notice that the quantities differ significantly on $\beta_i^j G_i^j$ $(i,j=r,c)$. By the nature of grouping, it is assumed $\beta_i^r \gg \beta_i^c$ $(i=r,c)$ so that $\beta_i^r \Lambda^r > \beta_i^c \Lambda^c$ $(i=r,c)$. Therefore, increasing θ^r (vaccination rate in risky group) would be more effective than uniform vaccination policy.

In this work, we divide the host into two groups for implementing vaccines effectively. However, in reality there may be no clearly well-defined line between the groups. Moreover, there may be more than two groups, differed by contact rates or risk factors, etc. The immunization campaign may be administered by giving priorities to the groups having higher risk factor. The population may be grouped in different ways, but we would emphasize the importance of some grouping before initiating vaccine campaign.

Our the group-strategic method in out model can be applied to implement vaccines or control measures in various infectious diseases, for example, influenza, measles or recently emerging ebola. In fact, the grouping strategy can be found in the current practice of vaccine distributions [5, 21] in some places and is shown to be effective against a possible outbreak [34]. In influenza, school-going children is considered to be the most targeted group, followed by the group of elderly individuals [10, 26]. Vaccinating healthy children against influenza can potentially reduce the rick of epidemic [10, 16, 20, 21]. It is found that by vaccinating 70% school-going children, the overall influenza infection can be reduced to below the epidemic level [21]. Children that possess less pre-immunity while encounter highest exposures are easy target of infectious disease. In addition to school-going children abd elderly people, pregnant women, individuals with critically illness and health workers could be other potential target groups. The group-strategic method can also be applied to HIV or sexually transmitted diseases (STDs). However, an appropriate model is required for STDs as our model (2) is, in general, not suitable for the STDs. An STD can be spread more rapidly in some particular groups such as sexual workers, men-sex-with-men group, injection-drug users and so on [4, 11]. These core groups should be given highest priority for allocating and implementing vaccines, should the HIV a vaccine becomes available.

Another grouping of the host can be made through regional basis. A disease may outbreak in a certain region with facile transmissibility and high case fatality, whereas individuals in some other regions may be relatively safer due to geographical distance and the environmental conditions. The recent outbreak of Ebola virus in West Africa, for example, threats with striking case fatality (50–90%) and transmissibility [9, 19, 23, 27] in that part of the world. The individuals surrounding the region are highly risky than those in the outer world. In this scenario, the individuals in that region should be vaccinated with utmost priority. Next preference may be given to the health workers of outer regions, since they are among the first line of exposures. As is

known, the first cases of Ebola reported outside West Africa are some nurses in the USA who got infected while caring an Ebola infected patient [28] from West Africa.

While this study offers some guidelines on vaccine implementations, our model has some limitations. We do not consider the behaviour change or the movement between the two groups. For simplicity, the model does not distinguish the infected population according to their disease progression (certain disease like HIV progress over the time) and uses a single transmission rate from all infected individuals. In our model (3), we do not distinguish the mode of transmission and population are not divided into sexes. In the case of sexually transmitted disease (STD), an individual can be infected through sexual contact or by sharing needles; other diseases, like flu or dengue, can be spread through airborne or vector-borne transmissions. We also ignore vertical transmission (mother to new born) and passive immunity to keep the model simple.

Finally, our goal is to find out an optimal vaccination strategy, not to demonstrate a rigorous analysis of a mathematical model. The formulation of the model (3) may underestimate or overestimate the real $\mathfrak{R}_o$. However, this estimate does not influence the consequences of the outcome of our analysis. That is, the proper estimation of $\mathfrak{R}_o$ does not violate the grouping idea; rather it helps group management. The model can be improved by incorporating several realistic aspects. For example, to assert on immunization we may further incorporate the delay and waning of vaccine immunity, imperfect vaccine efficacy and impact of vaccine complicacy. We leave these as possible future research projects.

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