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PARADOX OF VACCINATION PREDICTED BY A SIMPLE DENGUE DISEASE MODEL

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Abstract We consider here two types of vaccination in a host-vector transmission model for a dengue fever disease. We assume that the vaccine prevents vaccinated people from catching the disease caused by all types of dengue viruses but it is not perfect in which the vaccinated host may still suffer from the disease with a certain probability. The first type of vaccination is being administered constantly to a portion of newborn host. In this case the basic reproductive number remains the same and the vaccine will affect the eventual stages both for the disease-free equilibrium and endemic equilibrium. The second type of vaccination which is administered to general population is more complicated. In the case that the target people can be restricted to susceptible host, the vaccination directly affects the basic reproductive number. On the other hand, knowing that there is no practical way that infected people can be easily identified in the field, there is a chance that infected people may get vaccinated unintentionally. In this case the unintended vaccinated infected individual may stay longer in the infection stage. Assume that the vaccine affects the removal rate from infection stage with a certain retaining rate. We found a somewhat paradox result which reveals that increasing the portion

of vaccinated individuals will lead to the increase of the basic reproductive number, if the retaining rate of mistakenly vaccinated people is sufficiently larger than the effectiveness of the vaccine. Here we obtain the corresponding threshold number.

1. Introduction

Controlling the spread of dengue fever disease is regarded as one among the most important priorities of the World Health Organization's program, since the disease risks about 2.5 billion people all over the world, especially in the tropical countries [1]. A study [2] shows that the penetration of the disease into sub-tropical regions is also possible with the occurrence of global warming. This has attracted many scientists from many disciplines to undertake researches to uncover many phenomena, in order to control - or if possible to eliminate - the disease.

A standard program used in many countries to control the spread of the disease is the control of the main disease vector (*Aedes aegypti* mosquitos), for example by fuming or fogging. However, many studies show that this program was not fully effective. Many cases of dengue and dengue haemorrhagic fever still occur almost periodically in many urban areas. Fortunately, with the advancement of science and technology, the invention of vaccine for the dengue disease is now getting closer and closer [3, 4].

There are not many researchers who have investigated the effects of vaccination on the transmission of the infectious diseases, among them are [5, 6, 7]. In [5] the authors showed that a pulse vaccination strategy is effective to some extent to eradicate an epidemic. The researchers in [6] discussed the role of the vaccination failure to induce the development of the immune response in a disease outbreak. All of the researchers mentioned above work on a direct-transmitted disease. The effect of vaccination on an indirect-transmitted disease or on a vector-borne disease, such as dengue fever disease, has received little attention. The main objective of the present paper is to determine the level of vaccination effort required for eradicating the dengue disease, once a perfect vaccine is available. The vaccine is perfect if it can avoid the vaccinated individual from catching the dengue disease caused by all known types of virus. To address this issue we will develop a mathematical model similar

to our previous work with the inclusion of vaccination [8]. Further investigation taking into account the inaccuracy in selecting the target people for vaccination is shown below.

2. Host-Vector Model for Dengue Transmission

The transmission model for the dengue disease being used here is developed from the host-vector model in [9]. We briefly review the Host-Vector model of dengue fever transmission as follows. The model assumes that the host population $\mathcal{H}$ is constant, i.e. the death rate and birth rate are equal to μ_H. The vector population, which is in general very difficult to estimate, is also assumed to be constant $\mathcal{V}$. The host population is subdivided into the susceptible S_H, the infective I_H and the recovered, assumed immune, R_H. The vector population, due to a short life period, is subdivided into the susceptible S_V and the infective I_V. The interaction model [9] for the dengue transmission is given as follows

$$\begin{aligned}
\frac{dS_H}{dt} &= -\frac{bp_H I_V S_H}{\mathcal{H}} + \mu_H(\mathcal{H} - S_H) \\
\frac{dI_H}{dt} &= \frac{bp_H I_V S_H}{\mathcal{H}} - (\gamma + \mu_H) I_H \\
\frac{dI_V}{dt} &= \frac{p_V b I_H (\mathcal{V} - I_V)}{\mathcal{H}} - \mu_V I_V
\end{aligned} \tag{2.1}$$

where b is the vector biting rate, p_H is the transmission rate from infected vector to susceptible host, p_V is the transmission rate from infected host to susceptible vector, μ_V is the vector birth rate and γ is the removal rate of infected host to R_H. Writing the dynamic (2.1) in population proportion $S_h = \frac{S_H}{\mathcal{H}}$, $I_h = \frac{I_H}{\mathcal{H}}$ and $I_v = \frac{I_V}{\mathcal{V}}$, we have

$$\begin{aligned}
\frac{dS_h}{dt} &= -bp_H I_v \nu S_h + \mu_H - \mu_H S_h \\
\frac{dI_h}{dt} &= bp_H I_v \nu S_h - \gamma I_h - \mu_H I_h \\
\frac{dI_v}{dt} &= bp_V I_h - bp_V I_h I_v - \mu_V I_v
\end{aligned} \tag{2.2}$$

where $\nu = \frac{V}{H}$, which is the ratio between the vector population and the host population. There are two possible fixed points of (2.2) i.e. the non-endemic

equilibrium $(1,0,0)$ and the endemic equilibrium (S_{he}, I_{he}, I_{ve}), where

$$\begin{aligned} S_{he} &= \frac{p_V b\mu_H + \mu_V\gamma + \mu_V\mu_H}{p_V b(\mu_H + bp_H\nu)} \\ I_{he} &= \frac{\mu_H(b^2p_Vp_H\nu - \mu_V\gamma - \mu_V\mu_H)}{bp_V(\mu_H + bp_H\nu)(\gamma + \mu_H)} \\ I_{ve} &= \frac{\mu_H(b^2p_Vp_Hv - \mu_V\gamma - \mu_V\mu_H)}{(p_V b\mu_H + \mu_V\gamma + \mu_V\mu_H)\nu p_H b}. \end{aligned} \tag{2.3}$$

The non-endemic equilibrium is globally stable (see [9]) when $\mathcal{R} < 1$, where $\mathcal{R} = \frac{b^2p_Vp_Hv}{(\gamma+\mu_H)\mu_V}$. The non-endemic equilibrium becomes unstable and the stable endemic state appears when $\mathcal{R} > 1$. The basic reproductive number is (see [10]) $\mathcal{R}_o = \sqrt{\mathcal{R}}$. Although this model is too simple and not enough to simulate the transmission of the disease in the field, but it is good enough to understand the role of each parameters in the transmission process.

3. Reduction of Transmission Due to Vaccination

We consider two types of vaccination (see [11]), one that is being administered to a portion of new born host and another one is being administered to a portion of susceptible host. The main question here is whether it is enough to vaccine only new born host in order to control the spread of the disease or it is necessary to vaccinate the larger susceptible host. Further what are the consequences of the two types of vaccination, and what are the critical parameters which play critical role in the transmission process.

Let a portion ρ, $0 \leq \rho \leq 1$, of newborn host be vaccinated. Assume that the vaccine is not perfect and let the effectiveness of the vaccine is s, then $(1-\rho s)\mu_H\mathcal{H}$ newborns remain susceptible, and $\rho s\mu_H\mathcal{H}$ directly being removed to R_H. The corresponding dynamic of S_h is given by

$$\frac{dS_h}{dt} = -bp_H I_v S_h + \mu_H(1-\rho s)\mathcal{H} - \mu_H S_H \tag{3.1}$$

and the other two equations in (2.1) remain the same.

On the other hand when a portion σ, $0 \leq \sigma \leq 1$, of susceptible S_H are vaccinated, then the dynamics of both S_h and I_h are affected as follow

$$\begin{aligned} \frac{dS_h}{dt} &= -bp_H I_v v S_h(1-\sigma s) + \mu_H - \mu_H S_h \\ \frac{dI_h}{dt} &= bp_H I_v v S_h(1-\sigma s) - \gamma I_h - \mu_H I_h. \end{aligned} \tag{3.2}$$

Two cases (3.1) and (3.2) are written on one system, where either $\rho = 0$ or $\sigma = 0$, as follow

$$\begin{aligned}
\frac{dS_h}{dt} &= -bp_H I_v v S_h(1-\sigma s) + \mu_H(1-\rho s) - \mu_H S_h \\
\frac{dI_h}{dt} &= bp_H I_v v S_h(1-\sigma s) - \gamma I_h - \mu_H I_h \\
\frac{dI_v}{dt} &= bp_V I_h - bp_V I_h I_v - \mu_V I_v.
\end{aligned} \tag{3.3}$$

Further we rescale t by bp_v

$$\begin{aligned}
\frac{dx}{dt} &= \mu(1-r-x) - \eta x z \\
\frac{dy}{dt} &= \eta x z - \beta y \\
\frac{dz}{dt} &= y(1-z) - \delta z
\end{aligned} \tag{3.4}$$

where $r = \rho s$, $\mu = \frac{\mu_H}{bp_V}$, $\eta = \frac{p_H v(1-\sigma s)}{p_V}$, $\beta = \frac{\gamma+\mu_H}{bp_V}$ and $\delta = \frac{\mu_V}{bp_V}$. The system (3.4) has two possible equilibria, i.e. the non-endemic equilibrium $(1-r, 0, 0)$ and the endemic equilibrium (x_e, y_e, z_e), where

$$\begin{aligned}
x_e &= \frac{\mu(1-r)+\beta\delta}{\mu+\eta} = \frac{\mu_H bp_V - \mu_H \rho s bp_V + \mu_V\gamma + \mu_V\mu_H}{bp_V(\mu_H + p_H\nu b - p_H\nu b\sigma s)} \\
y_e &= \frac{\mu(\eta(1-r)-\beta\delta)}{(\mu+\eta)\beta} = \frac{\mu_H(p_H\nu p_V b^2(1-\rho s)(1-\sigma s) - \mu_V(\gamma+\mu_H))}{bp_V(\mu_H + bp_H\nu(1-\sigma s))(\gamma+\mu_H)} \\
z_e &= \frac{\mu(\eta(1-r)-\beta\delta)}{\eta(\mu(1-r)+\beta\delta)} = \frac{\mu_H(p_H\nu p_V b^2(1-\rho s)(1-\sigma s) - \mu_V(\gamma+\mu_H))}{bp_H\nu(1-\sigma s)(bp_V\mu_H(1-\rho s) + \mu_V(\gamma+\mu_H))}.
\end{aligned} \tag{3.5}$$

It is clear that the endemic equilibrium appears only when $\eta(1-r)-\beta\delta > 0$ or when $\mathcal{R}^* = \frac{\beta\delta}{\eta(1-r)} = \frac{p_H\nu p_V(1-\rho s)(1-\sigma s)b^2}{(\gamma+\mu_H)\mu_V} > 1$. Note that in the case of newborn vaccination, the number $\sqrt{\mathcal{R}^*}$ is not the *basic reproductive number*. This is because the dynamic of I_h and I_v are not affected by newborn vaccination. Rewriting $\mathcal{R}^* = (1-\rho s)(1-\sigma s)\mathcal{R}$, we have the reduction factor $(1-\rho s)(1-\sigma s)$. This gives the critical values of vaccination level in order to remove the endemic state.

The appearance of the endemic equilibrium, i.e. when $\mathcal{R}^* > 1$, corresponds to the change of stability of the non-endemic equilibrium as shown below. The characteristic polynomial of the non-endemic equilibrium is $(\lambda +$

$\mu)(\lambda^2(\beta+\delta)\lambda+\beta\delta-(1-r)\eta)=0$. This shows that the non-endemic equilibrium becomes unstable when $\mathcal{R}^*>1$ and the endemic state appears. The stability of the endemic equilibrium can be seen from it's characteristic polynomial

$$a_3\lambda^3+a_2\lambda^2+a_1\lambda+a_0=0 \tag{3.6}$$

where

$$\begin{aligned}
a_0 &= \beta\mu(\mu+\eta)(\eta-\eta r-\beta\delta)(\mu-\mu r+\beta\delta)\\
a_1 &= \mu\beta(\eta(1-r)-\beta\delta)(\mu(1-r)+\beta\delta)+\mu\beta^2(1-r)(\mu+\eta)^2\\
&+ \eta\mu(\mu+\eta)(1-r)(\mu(1-r)+\beta\delta)\\
a_2 &= \beta\mu(1-r)(\mu+\eta)^2+\beta\eta\delta(\mu(1-r)+\beta\delta)\\
&+ \left(\eta\mu(1-r)+\beta^2\eta+\beta^2\mu\right)(\mu(1-r)+\beta\delta)\\
a_3 &= (\mu-\mu r+\beta\delta)(\mu+\eta)\beta.
\end{aligned} \tag{3.7}$$

Note that all coefficients of the characteristic polynomial are positive. Direct calculation shows that

$$\begin{aligned}
a_1a_2 &> \mu^2\beta^2(\eta(1-r)-\beta\delta)(\mu(1-r)+\beta\delta)(1-r)(\mu+\eta)^2\\
&+ \mu\beta^3(1-r)(\mu+\eta)^2\eta\delta+\textit{positive terms}\\
&> \beta^2\mu(\mu+\eta)^2(\eta(1-r)+\beta\delta)(\mu(1-r)+\beta\delta)^2=a_0a_3.
\end{aligned} \tag{3.8}$$

We conclude this in the following theorem.

Theorem 3.1 *If $\mathcal{R}^*<1$, then the non-endemic equilibrium is globally stable and if $\mathcal{R}^*>1$ the (locally) stable endemic equilibrium appears. In order to remove the endemic state, the vaccination levels should satisfy $\rho>\frac{1}{s}(1-\frac{1}{\mathcal{R}})$ and $\sigma>\frac{1}{s}(1-\frac{1}{\mathcal{R}})$ respectively.*

Figures 1,2 and 3 give simulation for a non-vaccinated dynamic, newborn vaccination and general population respectively. Starting with 1 infective host in 10,000 host population with 90% susceptible and no infective vector.

No significant change is shown in the dynamics of newborn vaccination. The significance is shown only in the eventual dynamic at the endemic equilibrium (see figures 1 and 2). Direct reduction in the dynamic is shown in the general vaccination case (see figure 3). Numerical example ([11]) for perfect

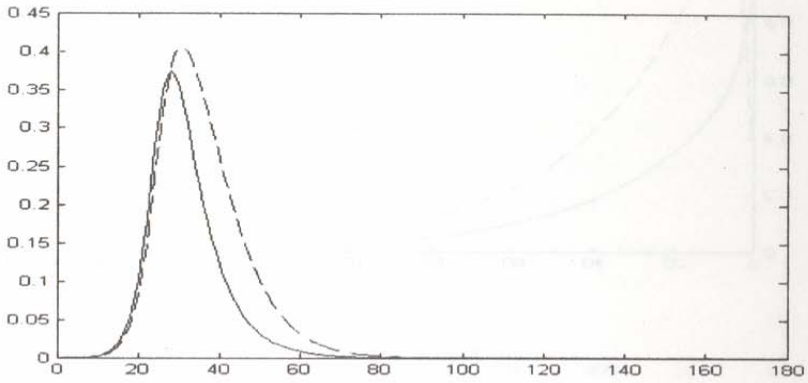

Figure 3.1.

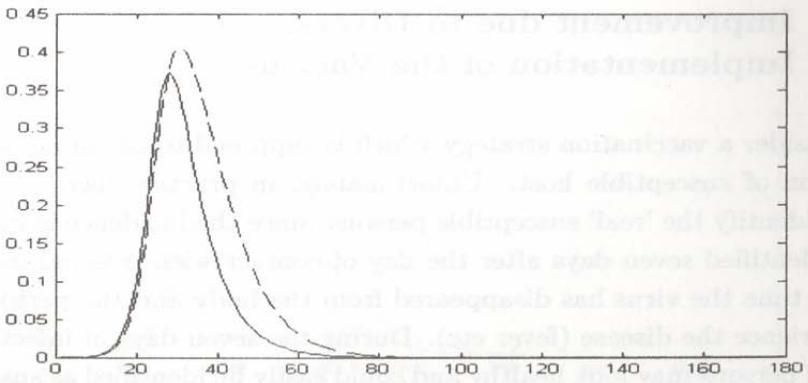

Figure 3.2.

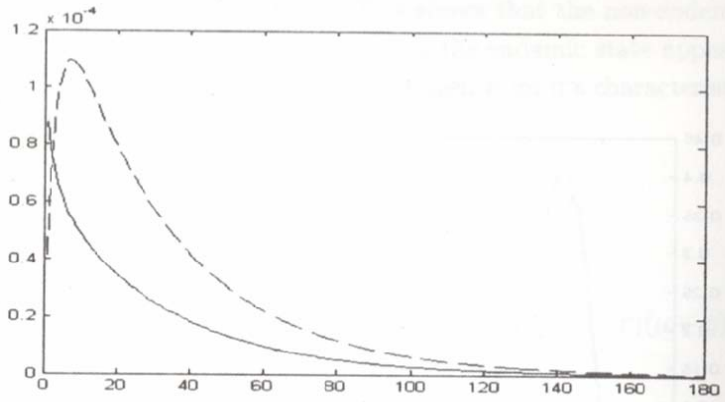

Figure 3.3.

vaccine shows that the newborn vaccination produces only a single outbreak and then followed by exponential decay of infective approaching toward the non-endemic(disease-free) equilibrium. Hence the effect of vaccination is to replace multiple outbreaks with a single outbreak. However if we apply the general vaccination, there is almost no outbreak occurs and the cases exponentially decay approaching the disease-free equilibrium.

4. Improvement due to Diversion in Implementation of the Vaccine

Consider a vaccination strategy which is supposed to be implemented to a portion of susceptible host. Unfortunately, in practice there is no easy way to identify the 'real' susceptible persons, since the incidence is in general being identified seven days after the day of contact with infected mosquito. By this time the virus has disappeared from the body and the person starts to experience the disease (fever etc). During the seven days of infection, the infected persons may look healthy and could easily be identified as susceptible person. Therefore it is natural to assume that there is a chance for infected persons to get vaccinated which may worsen the infection or delay the recovery of those persons. Suppose that the proportion σ of host being vaccinated are uniformly distributed among S_h, I_h and R_h, then the portion $\sigma\gamma I_h$ remains infected with the rate w. Therefore the dynamics are given below.

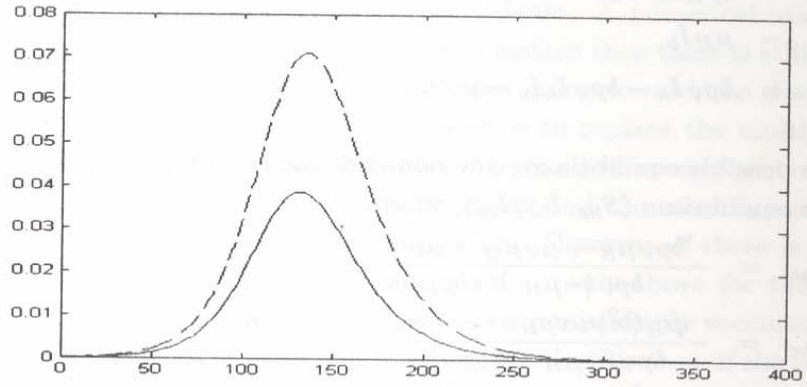

Figure 4.1.

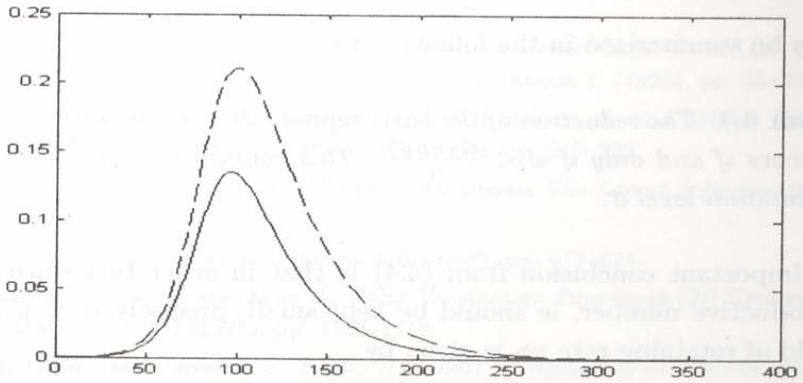

Figure 4.2.

$$\begin{aligned}
\frac{dS_h}{dt} &= -bp_H I_v v S_h(1-\sigma s) + \mu_H(1-S_h) \\
\frac{dI_h}{dt} &= bp_H I_v v S_h(1-\sigma s) - \gamma(1-\sigma)I_h - \gamma(1-\sigma)I_h - \sigma\gamma(1-w)I_h \\
&- \mu_H I_h \\
\frac{dI_v}{dt} &= bp_V I_h - bp_V I_h I_v - \mu_V I_v. \qquad (4.1)
\end{aligned}$$

Two possible equilibria are the non-endemic equilibrium $(1,0,0)$ and the endemic equilibrium (S_{he}, I_{he}, I_{ve}), where

$$\begin{aligned}
S_{he} &= -\frac{bp_V\mu_H + \mu_V\mu_H + \mu_V\gamma - \mu_V gm\sigma w}{bp_V(-\mu_H + vbp_H\sigma s - vbp_H)} \\
I_{he} &= -\frac{\mu_H(b^2p_V vp_H\sigma s - b^2p_V vp_H + \mu_V\mu_H + \mu_V\gamma - \mu_V\gamma\sigma w)}{bp_V(-\mu_H + vbp_H\sigma s - vbp_H)(-\mu - h - gm + \gamma\sigma w)} \\
I_{ve} &= \frac{\mu_H(b^2p_V vp_H\sigma s - b^2p_V vp_H + \mu_V\mu_H + \mu_V\gamma - \mu_V\gamma\sigma w)}{(\sigma s - 1)(bp_V\mu_H + \mu_V\mu_H + \mu_V\gamma - \mu_V\gamma\sigma w)p_H vb}. \\
& \qquad (4.2)
\end{aligned}$$

The endemic equilibrium S_{he}, I_{he}, I_{he} exists when

$$R_3 = \frac{p_v p_H v(1-\sigma s)b^2}{\mu_V\mu_H + \mu_V\gamma - \mu_V\gamma\sigma w} = P\mathcal{R}, \qquad (4.3)$$

where

$$P = 1 + \frac{\sigma(\gamma w - s(\gamma + \mu_H))}{\mu_H + \gamma(1-\sigma w)}. \qquad (4.4)$$

This can be summarized in the following theorem.

Theorem 4.1 *The reduction of the basic reproductive number in the dynamic (4.1) occurs if and only if* $w < \frac{s(\gamma+\mu_H)}{\gamma}$. *This condition does not depend on the vaccination level* σ.

An important conclusion from (4.4) is that in order to reduce the basic reproductive number, w should be kept small, precisely $w \leq w_o$, where threshold of retaining rate w_o is given by

$$w_o = \frac{s(\gamma + \mu_H)}{\gamma}. \qquad (4.5)$$

Figures 4 and 5 show the effect of the retaining rate w in the reduction of $\mathcal{R}$, when $w \leq w_o$ and $w \geq w_o$, respectively.

5. Conclusion

In this paper we discussed the effects of vaccination strategies on the dynamic of the transmission of dengue fever disease. A numerical example in [11] shows that, if we apply the newborn vaccination then there is still a single outbreak followed by exponential decay cases going toward the disease-free equilibrium. Hence the effect of vaccination is to replace the multiple outbreaks with a single outbreak. On the other hand if we apply the general vaccination, there is almost no outbreak occurs and the cases exponentially decay approaching the disease-free equilibrium. However, if there is a diversion in the implementation of the vaccine, the result above for the second strategy is misleading, if the retaining rate of the mistakenly vaccinated individuals is higher than the threshold number, W_c. In this case, if the retaining rate w is sufficiently larger than the effectiveness s of the vaccine, then increasing the portion of the vaccinated individuals will lead to the increase of the basic reproductive number. We call this phenomenon as a *paradox of vaccination*. In practice to avoid this paradox, there should be a screening program to identify the "false" susceptible individuals before vaccination is carried out.

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