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Review Article

Mathematical Model of Zoonotic NIPAH virus in South-East Asia Region

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Abstract

This paper deals with the dynamics of human infection from zoonotic NIPAH virus in South-East Asia region. A mathematical model of SEIR is formulated for human class without vaccination, and SEIRV is formulated for human class with vaccination and SIR model for animal class to describe the dynamics of NIPAH virus transmission and recovery based on with and without vaccination. It is known that till now no NIPAH vaccine has been developed, even though the research are going on to make vaccine to protect or prevent from NIPAH. The main aim is to analyze the effect of a vaccine in prevention and recovery from NIPAH. The basic reproduction number has been computed for both animal and human populations. The real parameters have been retrieved and further simulation-based experiments have been done to analyze the results. Simulations have been done for the models without vaccination and with vaccination to analyze the effects of vaccination on human population and found the vaccination would play a vital role for faster recovery and has control to mitigate the spreading infections.

Keywords: NIPAH; Infectious Diseases; South-East Asia; Global Stability Model

Introduction

After massive outbreak of NIPAH in Malaysia (1998), and sporadic outbreak in Bangladesh since 2001 to 2012, and in India NIPAH was sporadically outbreaking near west Bengal and Bordering of Bangladesh. But in 2018, it suddenly broke out in Kerala (May 2018), southern part of India that is very far (2,800 Km) from near the border of Bangladesh and an outbreak happened in recurring season.

As with the emergence of any new infectious disease in humans, the emergence of NIPAH requires exposure to the pathogen, successful infection of the hosts, and sufficient transmission between hosts to raise the basic reproductive number R above 1.8 The phylogenetic diversity of viral strains isolated from case samples suggests each of the outbreaks in Bangladesh was the result of a separate, distinct zoonotic disease transmission to the human population [1]. The phylogenetic distance of NiV from other pathogens in the Paramyxoviridae family suggests that Henipaviruses are ancient viruses with a long evolutionary association with their flying fox hosts [2]. Seroepidemiological surveillance of Pteropus giganteus, the sole Pteropid flying fox species in India and Bangladesh that meets the criteria for a wildlife reservoir species, demonstrated widespread evidence of NiV-B seroprevalence. Pteropus giganteus is a frugivorous colonial species, which is common in tropical regions of Southeast Asia. They aggregate in trees in permanent year round colonies of 100 or more and engage in a multi-partner mating strategy [3]. Tropical frugivorous flying foxes, like Pteropus giganteus, start reproducing at the onset of the rainy season, during which fruit abundance increases [4]. The species has low natural mortality, an annual reproductive event, and delayed onset of sexual maturity [5,6]. Pteropid bats with acute NIPAH viral infection display few clinical symptoms in laboratory

tests [7,8]. Transmission of maternal antibodies has been observed in captive flying foxes, though it is unclear whether transfer occurs trans placentally or via the mammary glands [9]. The foraging biology of flying foxes also has important implications for virus transmission. In order to ensure a constant food supply, flying foxes frequently migrate over large habitat areas. To avoid carrying unnecessary weight when flying, fruits are first chewed to extract nutrients while partially digested pulp and seeds are expectorated with a coating of saliva. Retrospective epidemiological studies suggest that the main routes for human infection include direct or indirect contact with flying fox secretions, such as urine or saliva, in roosting areas or in contaminated foodstuffs [10]. Ingestion of raw date palm sap has been repeatedly implicated as an infection source in Bangladesh [11]. Palm sap is usually processed at high temperatures to produce traditional sweeteners; however, the fresh juice is also drunk raw as a delicacy [12,13]. Sap harvesting occurs from mid-October through mid-March, which overlaps with the flying fox birth season and the seasonal outbreaks of NiV-B [14]. The process of date palm tapping causes the drain port to remain open which exposes it to air. Infrared cameras placed in orchards overnight confirm that Pteropus giganteus often feeds at tapping sites, which can lead to cross contamination [15].

Model Formation and parameter classifications

We divide the human population into four classes SEIR (Susceptible-Exposed-Infected-Recovered) and the bird population into three classes $S_bE_bI_b$ (Susceptible-Exposed-Infected).

Schematic flow of this model is shown in figure 2 and the state variables and associated parameters of this model are given in Table 1.

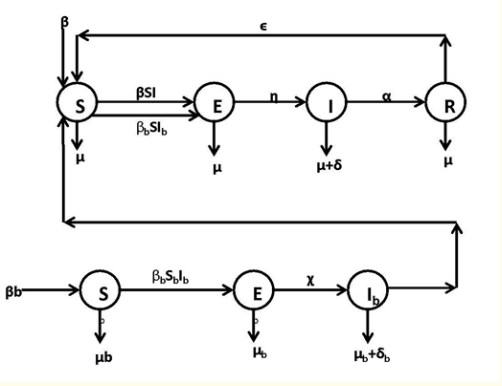

Figure 1

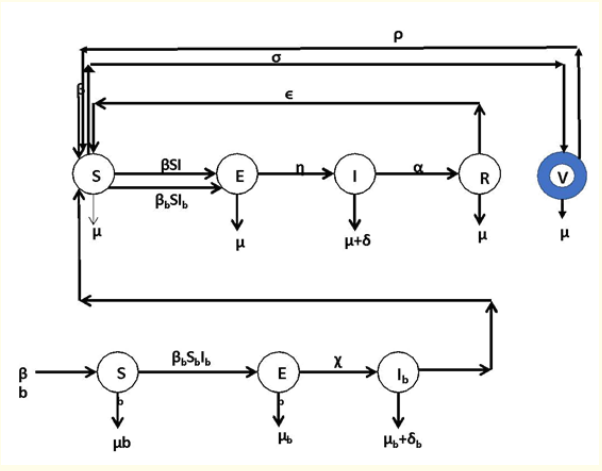

Figure 2

Abbreviations

SEIR: Susceptible-Exposed-Infected-Recovered in human populations

SbEbIb: Susceptible-Exposed-Infected in bird populations

RoH: Reproduction number in human populations

Rbo: Reproduction number in bird populations

Sh(t): Susceptible humans in time t

Eh(t): Exposed humans in time

tIh(t): Infectious humans in time

tRh(t): Recovered humans in time

tSb(t): Susceptible birds in time t

Eb(t): Exposed birds in time t

Ib(t): Infectious birds in time t

Nh(t): Total human population in time t

Nb(t): Total bird population in time t.

B: Birth rate of humans

Bb: Birth rate of birds

β: Infectivity of NIPAH virus and mutant NIPAH virus from human-to-human

βb: Infectivity of NIPAH virus from bird-to-bird or bird-to-animals

βbh: Infectivity of NIPAH virus from bird-to-human

η: Rate of transmission from exposed to infected humans

α: Rate of transmission from Infected to recovered humans

ε: Rate of transmission from recovered to susceptible humans

σ: Rate of Vaccinated humans

ρ: Rate of Vaccinated humans who are again suspected to diseases

X: Rate of transmission from exposed to infected birds

μ: Natural death rate of humans

δ: Death rate of humans due to NIPAH virus

μb: Natural death rate of birds

δb: Death rate of birds or animal class due to NIPAH virus

Model equations for humans population without Vaccination:

Based on the flow of transmission of avian influenza in human population as depicted in figure 2, we have the following system of equations:

$$\frac{dS}{dt} = BNh - \beta bh\, SI - \beta \quad SI_b + \varepsilon R - \mu S$$

$$\frac{dE}{dt} = \beta SI + \beta_{bh} SI_b - (\mu + \eta)\, E$$

$$\frac{dI}{dt} = \eta E - (\mu + \delta + \alpha)\, I \qquad \text{..... (1)}$$

$$\frac{dR}{dt} = \alpha I - (\varepsilon + \mu)\, R$$

Similarly, for the flow of transmission of avian influenza in birds population, we have a system of equations as:

$$\frac{dSb}{dt} = B_b N_b - \beta_b S_b I_b - \mu_b S_b$$

$$\frac{dE_b}{dt} = \beta_b S_b I_b - \mu_b E_b - \chi E_b \qquad \text{..... (2)}$$

$$\frac{dI_b}{dt} = \chi E_b - (\mu_b + \delta_b) I_b .$$

$$\text{And} \quad N_h(t) = S(t) + E(t) + I(t) + R(t)$$

$$N_b(t) = S_b(t) + E_b(t) + I_b(t) . \qquad \text{..... (3)}$$

Model equations for human's population with vaccination

$$\frac{dS}{dt} = BN_h - \beta SI - \beta_{bh} SI_b + \varepsilon R - \mu S - V + V$$

$$\frac{dE}{dt} = \beta SI + \beta_{bh} SI_b - (\mu + \eta)\, E$$

$$\frac{dI}{dt} = \eta E - (\mu + \delta + \alpha)\, I \qquad \text{..... (4)}$$

$$\frac{dR}{dt} = \alpha I - (\varepsilon + \mu)\, R$$

$$\frac{dV}{dt} = \sigma S - (\mu + \rho)\, V$$

Similarly, for the flow of transmission of avian influenza in birds population, we have a system of equations as:

$$\frac{dSb}{dt} = B_b N_b - \beta_b S_b I_b - \mu_b S_b$$

$$\frac{dE_b}{dt} = \beta_b S_b I_b - \mu_b E_b - \chi E_b \qquad \text{..... (5)}$$

$$\frac{dI_b}{dt} = \chi E_b - (\mu_b + \delta_b) I_b .$$

$$\text{And} \quad N_h(t) = S(t) + E(t) + I(t) + R(t) + V(t)$$

$$N_b(t) = S_b(t) + E_b(t) + I_b(t) . \qquad \text{..... (6)}$$

Stability of the model

In this section we find the basic reproduction number and stability of the model. We prove that our model is locally and globally stable for both diseases-free-equilibrium and endemic equilibrium points.

Basic reproduction number

For any epidemic model, the basic reproduction number is the average number of secondary infectious cases produced by a single infection in total susceptible population. Since all our model parameters are positive or non-negative, it is important to show that all state variables remain positive or non-negative for all positive initial conditions for t≥0. From our model equation we have

By solving equation (1) and (2), as well as for solving equation (4), and (5), we get the same reproduction number of human population and bird population as given below:

$$R_0^h = \frac{1}{S_h} = \frac{\eta(\beta + h)}{(\mu+\eta)(\mu+\delta+\alpha)} \qquad \text{..... (7)}$$

$$R_0^b = \frac{1}{S_b} = \frac{\chi\beta_b}{(\mu_b + \delta_b)(\mu_b + \chi)} \qquad \text{..... (8)}$$

Stability analysis of the model

Theorem 1 states that the systems 1 and 2 are locally asymptotically stable for the disease-free equilibrium, when $R_o^H < 1$ and $R^b_o < 1$.

Proof: Jacobian matrix of the system 1 and 2 without vaccination is as follows

$$J=\begin{vmatrix} -\mu & 0 & -\beta & \varepsilon & 0 & 0 & -\beta_{bH} \\ 0 & -(\mu+\eta) & \beta & 0 & 0 & 0 & \beta_{bH} \\ 0 & \eta & -(\mu+\delta+\gamma) & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -(\varepsilon+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_b & 0 & -\beta_b \\ 0 & 0 & 0 & 0 & 0 & -(\mu_b+\chi) & \beta_b \\ 0 & 0 & 0 & 0 & 0 & \chi & -(\mu_b+\delta_b) \end{vmatrix}$$

The eigenvalues of the Jacobian matrix J are calculated by T Block matrix. Diagonal matrix are

$$A_1 = \begin{vmatrix} -\mu & 0 \\ 0 & -(\mu+\eta) \end{vmatrix}$$

$$A_2 = \begin{vmatrix} -(\mu+\delta+\gamma) & 0 \\ \gamma & -(\varepsilon+\mu) \end{vmatrix}$$

$$A_3 = \begin{vmatrix} -\mu_b & 0 \\ 0 & -(\mu_b+\chi) \end{vmatrix}$$

$$A_4 = -(\mu_b+\delta_b)$$

So its eigenvalues are

$$\lambda_1 = -\mu$$
$$\lambda_2 = -(\mu+\eta)$$
$$\lambda_3 = -(\mu+\delta+\gamma)$$
$$\lambda_4 = -(\varepsilon+\mu)$$
$$\lambda_5 = -\mu_b$$
$$\lambda_6 = -(\mu_b+\chi)$$
$$\lambda_7 = -(\mu_b+\delta_b)$$

Hence all eigenvalues of the Jacobian matrix J are negative when $R_o^H < 1$ and $R^b_o < 1$.

This proves that the system of SEIR for the human population and the system of SbEbIb for bird population are locally asymptotically stable when $R_o^H < 1$ and $R^b_o < 1$.

Jacobian matrix of system (4) and (5) with vaccination are as below

$$J_v=\begin{vmatrix} -\mu & 0 & -\beta & \varepsilon & (\rho-\sigma) & 0 & 0 & -\beta_{bH} \\ 0 & -(\mu+\eta) & \beta & 0 & 0 & 0 & 0 & \beta_{bH} \\ 0 & \eta & -(\mu+\delta+\gamma) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -(\varepsilon+\mu) & 0 & 0 & 0 & 0 \\ \sigma & 0 & 0 & 0 & -\mu+\rho) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_b & 0 & -\beta_b \\ 0 & 0 & 0 & 0 & 0 & 0 & -(\mu_b+\chi) & \beta_b \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -(\mu_b+\delta_b) \end{vmatrix}$$

The eigenvalues of the Jacobian matrix J_v are calculated by block matrix. Diagonal matrix are

$$A_{v1} = \begin{vmatrix} -\mu & 0 \\ 0 & -(\mu+\eta) \end{vmatrix}$$

$$A_{v2} = \begin{vmatrix} -(\mu+\delta+\gamma) & 0 \\ \gamma & -(\varepsilon+\mu) \end{vmatrix}$$

$$A_{v3} = \begin{vmatrix} -(\mu_b+\rho) & 0 \\ 0 & -\mu_b \end{vmatrix}$$

$$A_{v4} = \begin{vmatrix} -(\mu_b+\chi) & \beta_b \\ 0 & -(\mu_b+\delta_b) \end{vmatrix}$$

So its eigenvalues are

$$\lambda_{v1} = -\mu$$
$$\lambda_{v2} = -(\mu+\eta)$$
$$\lambda_{v3} = -(\mu+\delta+\gamma)$$
$$\lambda_{v4} = -(\varepsilon+\mu)$$
$$\lambda_{v5} = -(\mu+\rho)$$
$$\lambda_{v6} = -\mu_b$$
$$\lambda_{v7} = -(\mu_b+\chi)$$
$$\lambda_{v8} = -(\mu_b+\delta_b)$$

Hence the model with vaccination all eigenvalues of the Jacobian matrix J_v are negative when $R_o^H < 1$ and $R^b_o < 1$.

This proves that the system with vaccination SEIRV for human population are locally asymptotically stable when $R_o^H < 1$ and $R^b_o < 1$.

Global stability of disease-free equilibrium

We show the global stability of the model given by Kongang and Sollel (8). In this method to show global stability, the model has to satisfy the five hypothesis which has been summarized briefly in the appendix. Theorem 3 states that system 1, 2, 4, and 5 are globally stable for disease-free equilibrium when $R_o^H \leq 1$ and $R^b_o \leq 1$.

Proof: we have shown above that $D = [(S, E, I, R, S_b, E_b, I_b) \varepsilon R^7_+ : N_H \leq \mu\beta, N_b \leq \mu_b\beta_b]$

Is bounded and positively invariant in R^7_+ where the hypothesis A_1 and A_2 are satisfied.

In our model

x1 = (S, R, Sb)

x2 = (E, I, Eb, Ib)

The matrix $A_2(x)$ is given by

$$\begin{vmatrix} -(\mu+\eta) & \beta S & 0 & \beta_{bH} S_b \\ \eta & -(\mu+\delta+\gamma) & 0 & 0 \\ 0 & 0 & -(\mu_b+\chi) & \beta_b S_b \\ 0 & 0 & \chi & \mu_b \delta_b \end{vmatrix}$$

As required by the hypothesis H_3, for any $x \varepsilon R^7+$ the matrix is irreducible. Now, for hypothesis H_4, there is a maximum and uniquely realized in R^7+ if S = 1 and S_b = 1 at DFE. This maximum matrix is J_2, the block of the Jacobian at DFE, corresponding to the matrix $A_2(x)$ is given by

$$J_2 = \begin{vmatrix} -(\mu+\eta) & \beta & 0 & \beta_{bH} \\ \eta & -(\mu+\delta+\gamma) & 0 & 0 \\ 0 & 0 & -(\mu_b+\chi) & \beta_b \\ 0 & 0 & \chi & -(\mu_b+\delta_b) \end{vmatrix}$$

For hypothesis H_4 the diagonal block matrix

$A^-_{11}{}^2$ and $A^-_{22}{}^2$ are bounded by the matrices

$$A^-_{11}{}^2 = \begin{vmatrix} -(\mu+\eta) & \beta \\ \eta & -(\mu+\delta+\gamma) \end{vmatrix}$$

and

$$A^-_{22}{}^2 = \begin{vmatrix} -(\mu+\chi) & \beta_b \\ \chi & -(\mu_b+\delta_b) \end{vmatrix}$$

Which are maximum. This maximum is realized at each point of manifolds $M_1(E = 0, I = 0)$ and $M_2(E_b = 0, I_b = 0)$. This implies that these points belong to the manifold with equations.

E = I = Eb = Ib = 0. Thus the hypothesis H4 is satisfied.

Now for the hypothesis H_3, the condition $\gamma(A^-_{11}{}^2) \leq 0$ and $\gamma(A^-_{22}{}^2) \leq 0$ can be expressed as.

$$\frac{\beta H}{(\mu+\eta)(\mu+\delta+\gamma)} \leq 1$$

And

$$\frac{\beta_b \chi}{(\mu_b+\chi)(\mu_b+\delta_b)} \leq 1$$

Thus the hypothesis H_5 is equivalent to $R_o^H \leq 1$ and $R^b_o \leq 1$. This proves that the model is globally stable for disease-free equilibrium when $R_o^H \leq 1$ and $R^b_o \leq 1$.

Numerical simulations and effect of parametric values

In this section, using Runge-kutta-Fehlberg method of order 4 and 5, we numerically simulate our system (1) and (2) with real parametric values as given in Table 2 and also establish the stability of models by taking different examples. MATLAB is used to simulate the systems.

	Malaysia	Bangladesh	India
B	1000	1000	1000
Bb	300	300	300
B	0.0253	0.0188	0.019
Bb	0.5	0.12	0.12
β	0.08	0.08	0.08
β_b	0.5	0.5	0.5
$^{\beta}$bh	0.75	0.65	0.5
η	0.59	0.86	0.86
α	0.5949	0.22457	0.2627
ε	0.0001	0.0001	0.0001

Table 1

χ	0.6	0.6	0.6
μ	0.0051	0.00543	0.0073
μ_b	0.125	0.025	0.025
δ	0.4	0.77	0.73
δ_b	0.24	0.54	0.54
σ	0.1 to 0.99	0.1 to 0.99	0.1 to 0.99
ρ	0.08	0.08	0.08
R_0(h)	0.8228891	0.72541973	0.57511818
R_0(b)	1.13367974	0.84955752	0.84955752

Table 2

Example 1

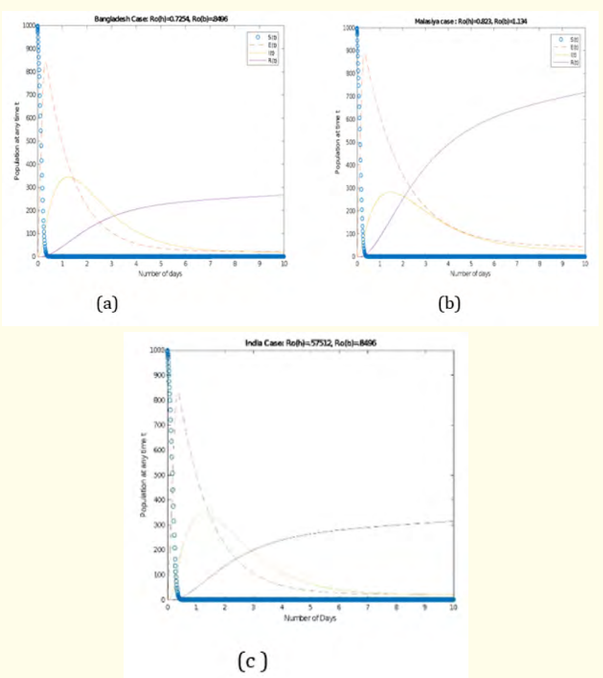

Figure 3 (a): Data of NIPAH virus cases in Bangladesh; **(b):** Data used of NIPAH virus cases in Malaysia; **3(c):** Data used of NIPAH virus cases in India.

The figure 3(a), 3(b), and 3(c) clearly indicates from nature of trajectory the recovery rate is higher in Malaysia case compare to Bangladesh and India. The trajectory of Infectivity is still showing asymptotic nature that is very true as the recovery time from brain encephalitis is not known.

Example 2

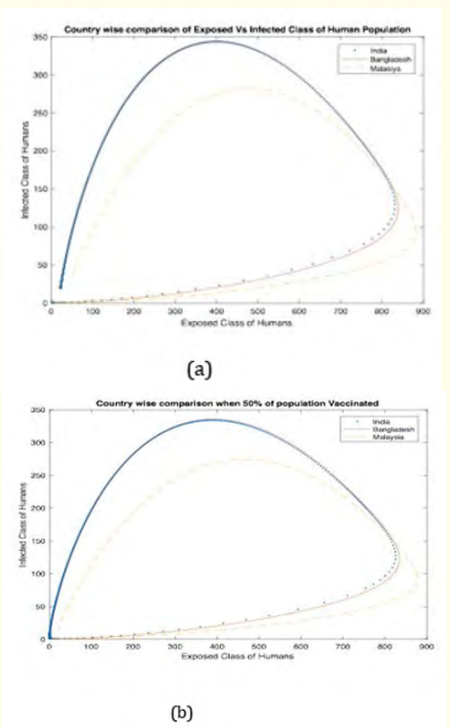

Figure 4

The nature of trajectory is similar in figure 4(a), and 4(b) both cases with and without vaccination. It indicates that the chances of getting exposed and infective are similar but little bit reduction in infectious class. It also indicates that the complete recovery time is 5 to 8 days with vaccination, and about 6% of infectious class population will face encephalitis for long time without vaccination.

NIPAH cause of encephalitis that is a long-term disorder for any person. The nature of trajectory in figure 5(a), and 5(b) clearly indicates the vaccination would be able to mitigate the severity of infections that cause encephalitis, as well as it will reduce the number of people become infectious. Without vaccination 6% of Infectious people will still face encephalitis.

Example 3

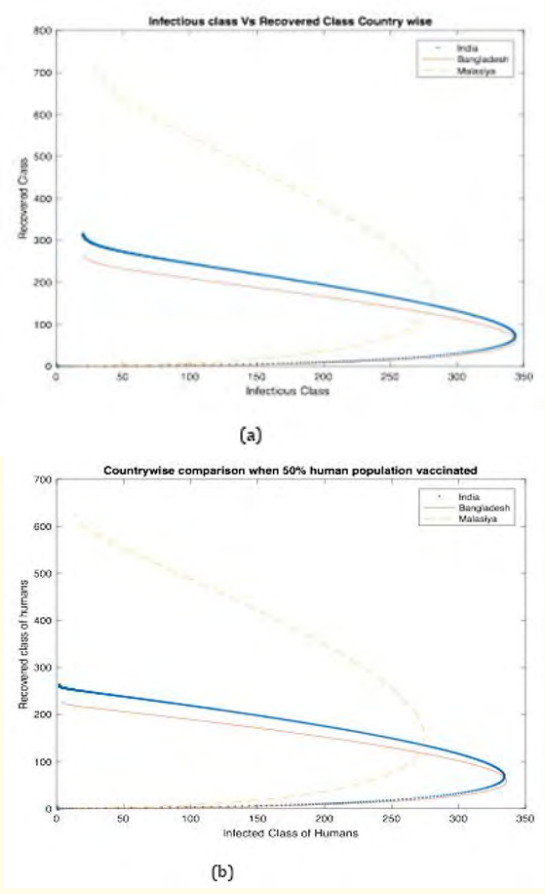

Figure 5

Example 4

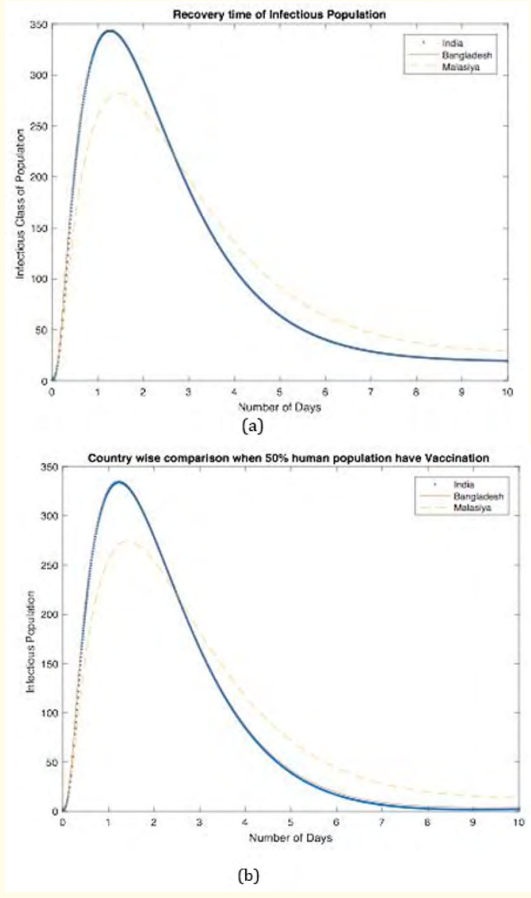

Figure 6

It is clear from figure 6(a) that with basic support recovered population would have longer recovery time due to encephalitis, and from figure 6(b) it clearly indicates that if 50% of the population get vaccinated, then chances of brain encephalitis would be minimal, and so the vaccination would be able to mitigate the severity of infections due to NIPAH virus. The complete recovery time is 5 to 8 days.

Conclusion

By using the SEIR, SERV and SIR models we are able to properly extrapolate the outcome of the overall health and survivability of a population that has been vaccinated and a population that are unvaccinated. When comparing the outcomes of the two populations we can easily conclude that a vaccinated population had a better survivability rate and lower transmission rate compared to that of

the unvaccinated population. This is obvious, however the important outcome that differs a lot between the two populations is the secondary infections that follow after a population has recovered from the NIPAH. The unvaccinated population had a higher risk of getting encephalitis later in life compared to that of the vaccinated population. By factoring into account this secondary disease that appears due to NIPAH we can clearly see that in South-East Asia the population later in life will be much more susceptible to encephalitis which brings the overall health of the population down and also increases the mortality rate of NIPAH, due to NIPAH being a direct factor of contracting encephalitis.

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