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Model and control strategy of the deadly nipah virus (NiV) infections in Bangladesh

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ABSTRACT

Recent outbreaks of deadly nipah virus (NiV) causing serious human epidemic disease have been one of the most alarming concerns in the public health of Bangladesh. NiV is a newly detected highly pathogenic virus with ability to cause devastating morbidity and mortality (an estimated 100% in some cases) rate among the human populations. This emerging infectious disease has become the most alarming threats of the public healths not only in Bangladesh but also in the world mainly due to its periodic outbreaks (as it strikes almost every year) and the highly devastating mortality rate. The aim of this paper is firstly to investigate the disease propagation and control strategy of NiV infections and secondly to analyze a mathematical model of the SIR-type epidemic disease of this deadly virus in the form of ordinary differential equations (ODEs). The behavior of the dynamics of NiV infections has been illustrated by the numerical simulations.

KEYWORDS

Nipah virus;
Infectious disease;
SIR-type model;
Numerical analysis;
Control strategy.

INTRODUCTION

Bangladesh has been the most risky geographic distribution for several epidemic and infectious diseases like the newly detected deadly nipah virus (NiV) infections in the southeast region of Asia[20]. The very recently occurred and even periodical outbreaks of nipah virus infections indicate the serious alarming and devastating threats of the public healths in Bangladesh as well in the world. The outbreaks of NiV infections in Bangladesh are assumed to be the most alarming and thus the significantly different in epidemiologic and clinical features[4] because of the fact that it has been occurring every year (except 2002 and 2006) since the first detection of nipah virus and its devastating infections in Bangladesh in 2001. Ten outbreaks have already occurred from the years 2001 to 2012, causing 145 deaths among the identified 185 as seriously infected by NiV with the average mortality rate of 79% (see TABLE 1). A statistics of the chronological outbreaks of NiV infections and the increasing average mortality rate is shown in TABLE 1. From the TABLE 1 we see that only in the years 2011 and 2012, the mortality rate is 100% which is of course a great threat for the global public health along with Bangladesh. However, steps for proper treatments and control strategies should be taken immediately right now. Although significant numbers of research have been carried out individually and/

or jointly in the Institute of Epidemiology, Disease Control and Research (IEDCR) and the International Center for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) with the other national and international collaborations on this deadly virus and mentionable research works have been published in the internationally reputed journals, the world health expertise should pay special attention to end this highly fatal disease for ever from Bangladesh. Otherwise it may pose a significant threat to global health if the outbreaks become more widespread with an average mortality rate of 79%, since this is a virus that is devastating to the families affected. We refer readers to ([7,10,14-16] and the references within) for the more details on NiV infections as well as some recent developments. Some other infectious diseases such as HIV/AIDS[2,3], dengue, swine flu, etc. are also of great concerns of public healths in Bangladesh as well as in the world.

Our aim in this paper is mainly to formulate the dynamics of NiV infections in mathematical models in the form of ordinary differential equations. We solve the models by numerical simulation and then analyze the behavior of the disease dynamics. Before going to our model analysis it is worth presenting a brief discussion on NiV infections and disease transmissions for the readers convenient .

What is NiV?

NiV, of the family *Paramyxoviridae* and the genus *Henipavirus*, is a *zoonotic* (as it is transmitted from animals to humans) virus that causes outbreaks of fatal encephalitis in humans[4]. The human NiV infection was first recognized in a large outbreak of 276 reported cases in peninsular Malaysia and Singapore from September 1998 through May 1999 (see for examples[3,6,11,18]). The virus was first isolated from a patient from Sungai Nipah village in Malaysia and the name 'Nipah' was first introduced according to the name of that village. Most of the cases presented primarily with encephalitis and mortality rate of 39%, had close contact with sick pigs[21,22], which indicates that the host of NiV infections in 1998 at Malaysia outbreaks was the pigs. However, large fruit bats of the genus *Pteropus* appear to be the natural reservoir of NiV and the pigs are assumed to be infected from those fruit bats. The possible ways of how the pigs might be infected from the fruit rats in Malaysian outbreaks were discussed in[11].

NiV outbreaks in Bangladesh

After two years of NiV outbreaks, no further outbreaks occurred in Malaysia. Unfortunately new outbreaks of NiV infections in Bangladesh were initiated in 2001, which continue until today. Since the first detection of NiV in 2001, ten outbreaks have already been occurred in Bangladesh with highly mortality rate an estimated 79% in an average and 100% in some cases (see TABLE 1).

TABLE 1 : Outbreaks of nipah virus infections in Bangladesh, 2001–2012[18].

Outbreaks (Years)	No. of Infected People	No. of Deaths	Percentage (%)
2001	13	9	69
2002	0	0	0
2003	12	8	67
2004	67	50	75
2005	12	11	92
2006	0	0	0
2007	20	13	65
2008	10	9	90
2009	4	1	25
2010	17	15	88
2011	24	24	100
2012	6	6	100
Total	185	145	79

The most alarming fact is that almost every year in winter (December to March), the deadly NiV stroke in the northern and western regions of Bangladesh. The mode of transmissions of NiV infections in Bangladesh is quite different in comparison to that in Malaysia as reported in[7]. In Malaysian outbreaks, NiV was transmitted to human via the sick pigs. Since the natural reservoirs of nipah virus are fruit bats, so the pigs are supposed to become infected by eating fruits partially eaten and thus contaminated by the fruit bats with their urine and saliva. However, NiV outbreaks in Bangladesh remain devastating because of the mode of transmissions. In the early stage, nipah virus is supposed to be transmitted through the date palm sap from its natural reservoirs, i.e., fruit bats in addition to the case discussed above. When people drink the contaminated date palm sap, they become infected by the nipah virus. Once people have been infected by the NiV either by eating the partially eaten and contaminated fruits or by drinking the contaminated raw date palm sap, the virus

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spreads into human to human because of its serious infectivity. At least one case was reported[19] that a doctor died due to NiV infection while giving the healthcare to a NiV infected patient in hospital. A schematic diagram of possible nipah virus transmissions in Bangladesh is shown in Figure 1.

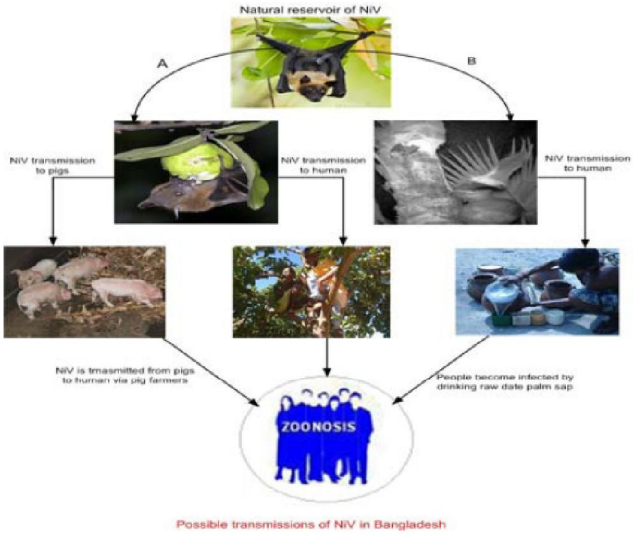

Figure 1 : A schematic diagram of possible nipah virus transmissions in Bangladesh[16].

From the Figure 1, we see that *case A* was the only mode of NiV transmissions in Malaysia outbreaks, whereas both *case A* and *case B* are the modes of NiV transmissions in Bangladesh. The bad news is that the transmission does not end here. When NiV is somehow transmitted to human, it continues to be transmitted from human to human and thus the whole family can be affected by this deadly virus, if proper and careful treatments as well as control measures are not followed.

TREATMENTS AND CONTROL

There is a well-known proverb that '*Prevention is better than Cure*'. This proverb is still the key measure for the treatments of NiV infections. As NiV is a recently detected highly emerging deadly virus, no proper drugs and even effective vaccines are available for the treatment of such types of infectious diseases. So a complete cure by treatments using drugs and/or vaccines is still a dream, although some drugs are under investigations and a vaccine is being developed[20]. However, a research shows that *ribavirin*, an antiviral drug is able to reduce the mortality of acute Nipah encephalitis[8]. The effective preventive and control measures can only reduce the spreads of nipah infections. That is an intensive supportive care with treatment of symptoms is the main approach to managing the infection in the infected humans. For effective preventive and control measures to reduce the risk of infections in people, the following three cases must be followed:

Bat-to- human transmission

This transmission can be prevented by decreasing bat access to date palm sap. Also freshly collected date palm juice should also be boiled and fruits should be thoroughly washed and peeled before consumption.

Human-to-human transmission

This transmission can be reduced by avoiding close physical contact with Nipah virus-infected people. In this case gloves and protective equipment should be worn when taking care of ill people and regular hand washing should be carried out after caring for or visiting sick people.

Animal-to-human transmission

Prevention of this transmission requires that gloves and other protective clothing should be worn while handling sick animals or their tissues, and during slaughtering and culling procedures.

Finally, in the absence of a vaccine, the only way to reduce infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the virus. We refer reader to[14-16,18-20,23] and references within for more details about the prevention and control strategies of NiV infections.

We are now in position to formulate the mathematical model of the dynamics of NiV infections. The analysis of disease dynamics can help us identifying the better strategy to control the infections.

MATHEMATICAL MODEL

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. An efficient preventive and control measure of the spread of a life-threatening pathogen mainly depends on an essential understanding the mechanisms of that pathogen. Mathematical models of infectious diseases in human have been used to increase our understanding of these mechanisms and to test hypotheses about ef-

fective methods for prevention and control of infectious diseases in humans. The transmission interactions in a population are very complex, so it is difficult to comprehend the large scale dynamics of disease spread. Understanding these interaction characteristics can lead to better approaches to decreasing the transmission of diseases. Mathematical models are used in such comparing, planning implementing, evaluating, and optimizing various detection, prevention, therapy and control programs. We recall that NiV is a newly detected highly emerging pathogen and no proper drugs and/or vaccines are available yet for its treatments. So, it is essential for the physicians and biologists to understand the disease mechanisms in the human body in order to find out effective methods for prevention and control.

Human NiV is a *zoonotic* virus and thus transmitted first from animal to human. Once it has been transmitted to human, then it continues to be transmitted through human to human (H2H) by the closed contact of infected individuals due to its highly infectivity. So the dynamics of NiV infections can be described by a *SIR-type* infectious disease model in the form of a set of ordinary differential equations (ODEs). Let us suppose that S (t), I (t), and R (t) denote the number of individuals in the susceptible, infectious, and recovered classes at time t. The total population at time t is represented by N(t) = S(t)+I(t)+R(t). The susceptible (S) individuals are those able to be infected by the disease parasite. It is assumed that all people are susceptible by born. The infectious (I) individuals are those who are infected and able to transmit the parasite to others and the recovered (R) individuals are those who have recovered and thus are immune or have died from the disease and do not contribute to the transmission of the disease. We formulate and analyze two basic SIR models and discuss the behavior of the propagation of diseases in two different contexts: one is *Epidemic model* while the other is *Endemic model*.

Basic SIR epidemic model

The basic SIR epidemic models are used to describe rapid outbreaks that occur in a short duration of time (e.g. less than one year). Since the time period is short, no vital dynamics (births and deaths) are considered in this model. The deterministic model for the single outbreak as in[1] (see also[12] and[13]) can be represented by the following ordinary differential equations:

$$\begin{aligned}\dot{S}(t) &= -\beta\frac{S(t)I(t)}{N}\\ \dot{I}(t) &= \beta\frac{S(t)I(t)}{N} - \alpha I(t) - \gamma I(t)\\ \dot{R}(t) &= \gamma I(t)\end{aligned} \quad \textbf{(1)}$$

with the boundary conditions

$$S(0) = S_0 \geq 0,\ I(0) = I_0 \geq 0,\ R(0) = R_0 \geq 0$$

Basic SIR endemic model

The basic SIR endemic models are used for studying diseases over longer periods, during which there is a renewal of susceptibles by births or recovery from temporary immunity. So the basic deterministic endemic model is the SIR model with vital dynamics (i.e. inclusions of births and deaths) given by

$$\begin{aligned}\dot{S}(t) &= \mu N - \mu S(t) - \beta\frac{S(t)I(t)}{N}\\ \dot{I}(t) &= \beta\frac{S(t)I(t)}{N} - (\alpha+\gamma+\mu)I(t)\\ \dot{R}(t) &= \gamma I(t) - \mu R(t)\end{aligned} \quad \textbf{(2)}$$

with the boundary conditions

$$S(0) = S_0 \geq 0,\ I(0) = I_0 \geq 0,\ R(0) = R_0 \geq 0$$

This SIR model (2) is almost the same as the SIR epidemic model presented in (1) above, except that it has an inflow of newborns into the susceptible class at the rate μN and deaths in the classes at rates μS, μI, and μR. The deaths balance the births so that the total population size N is constant. We assume that the mean lifetime $\frac{1}{\mu}$ would be about 60 years in Bangladesh.

Both in model (1) and (2), β is the incident coefficient representing the average rate of adequate contacts (i.e., contacts sufficient for transmission) of a person per unit time, then $\frac{\beta I}{N}$ is the average number of contacts with infected individuals per unit time of one susceptible, and $\frac{\beta IS}{N}$ is the number of new cases per unit time due to the susceptibles. This form of the *horizontal incidence* is called the *standard incidence* (see for details[12]).

The simple mass action law ηIS, with η as a mass action coefficient, is also sometimes used for the horizontal incidence. In this case the parameter η has no

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direct epidemiological interpretation[8], but comparing it with the standard formulation, it shows that $\beta = \eta N$, so that this form implicitly assumes that the contact rate β increases linearly with the population size N. However, it is shown in[12,13] that the *standard incidence* is more realistic for human diseases than the simple mass action incidence. The term γI represents the recovery rate with the *recovery coefficient* γ and α is the disease induced death rate[1].

The basic concepts as well as the fundamental questions of epidemiological modeling are the *threshold* conditions that determine whether an infectious disease will spread or will die out into a population. In this regard, a key epidemiological quantity R_0, called the *basic reproductive ratio* plays the significant role in analyzing the diseases behavior of the model. R_0 is the number of secondary cases that result from a single infectious individual in an entirely susceptible population. Another threshold quantity is the *contact number*, σ, where $\sigma = \frac{\beta}{\gamma}$ is defined by the *contact rate* β per unit time multiplied by the average infectious period $\frac{1}{\gamma}$. In most cases, the basic reproductive number and contact number are the same. So in our models, the basic reproductive ratio is taken as $R_0 = \sigma = \frac{\frac{\beta S_0}{N}}{\alpha+\gamma} \approx \frac{\beta}{\alpha+\gamma}$ (for the model (1)) and $R_0 = \sigma = \frac{\frac{\beta S_0}{N}}{\alpha+\gamma+\mu} \approx \frac{\beta}{\alpha+\gamma+\mu}$ (in case of model (2)) under the assumption that $S_0 \approx N$. The current usage of R_0 is the following: if $R_0 < 1$, the modeled disease dies out, and if $R_0 < 1$, the disease spreads in the population. Reproductive ratios turned out to be an important factor in determining targets for vaccination coverage and/or control measurements. However, we show these analyses in the next section.

The models presented in (1) and (2) are the special cases of SEIR models, where the exposed classes in a latent period are absents. The mathematical models and control strategies of such SEIR models can be found in[4] and[17] (see also[3]).

NUMERICAL SIMULATIONS

We perform numerical simulations of our models proposed both in (1) and (2) by the *ODE-solver* using *MATLAB* programming. First we solve the epidemic model (1) considering the initial values S(0) = 1000, I(0) = 5, R(0) = 0 and the values of the parameters $\alpha=0.15$, $\gamma=0.75$, $\beta=0.1$. The result of the simulations of the individual classes is presented in Figure 2(a) and the infectious population class is in Figure 2(b). The Figure 2(b) shows that an epidemic occurs and the disease persists in the population since the basic reproductive number $R_0 = 3 > 1$. Now we solve the model (1) taking the parameter $\beta = \frac{0.75}{4}$ with all other values same as before and the simulations of susceptible class and infectious class are shown in Figure 3(a) and Figure 3(b) respectively. A straightforward comparison between Figure 2(b) and Figure 3(b) shows that the disease dies out in the population as the basic reproductive number $R_0 = 0.75 < 1$ (see Figure 3(b)). Now, we run the simulations of the endemic model (2) taking the demography (births and deaths) into account. In this case, we take the values of the parameters as $\alpha = 0.15, \gamma = \frac{1}{3}, \beta = 1.5, \mu = \frac{1}{60}$ and the result of the simulations for the individual population classes is pre-

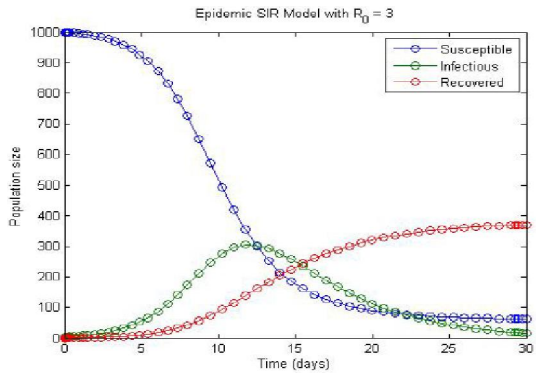

Figure 2(a) : Population sizes for the epidemic model (1) with the basic reproductive number $R_0 = 3$.

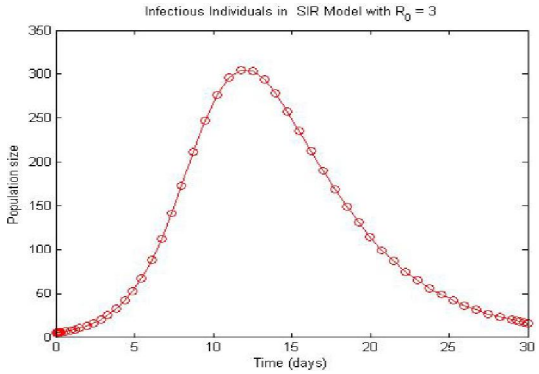

Figure 2(b) : Infectious individuals for the epidemic model (1) show the persistence of the disease in the population.

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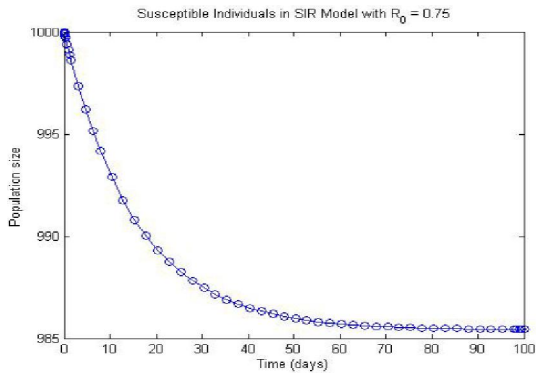

Figure 3(a) : Susceptible individuals for the epidemic model (1) with the basic reproductive number R_0 = 0.75.

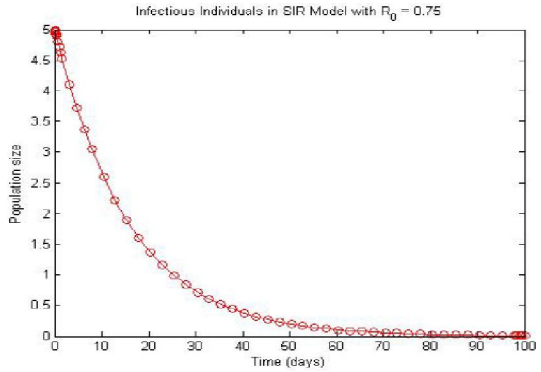

Figure 3(b) : Infectious individuals for the epidemic model (1) show that the disease dies out in the population.

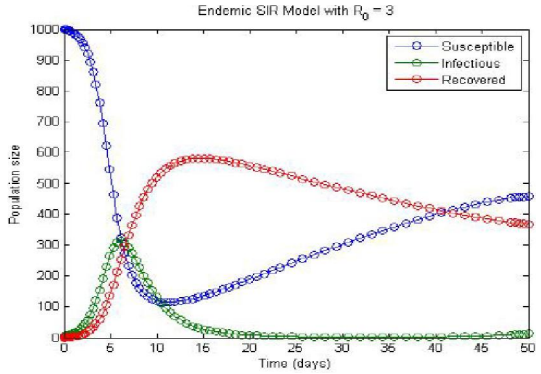

Figure 4(a) : Population sizes for the endemic model (2) with the basic reproductive number R_0 = 3.

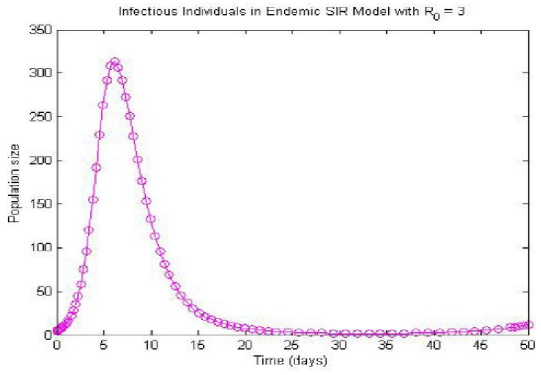

Figure 4(b) : Infectious individuals for the endemic model (2) with the basic reproductive number R_0 = 3.

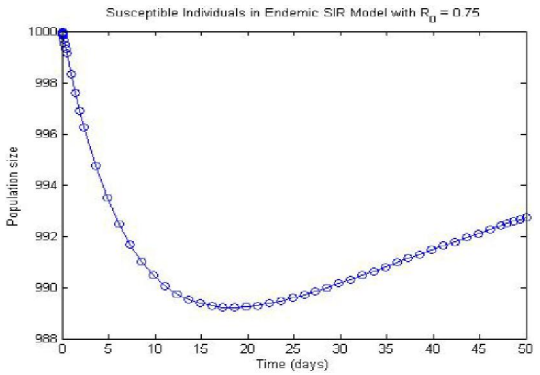

Figure 5(a) : Susceptible individuals for the endemic model (2) with the basic reproductive number R_0 = 0.75.

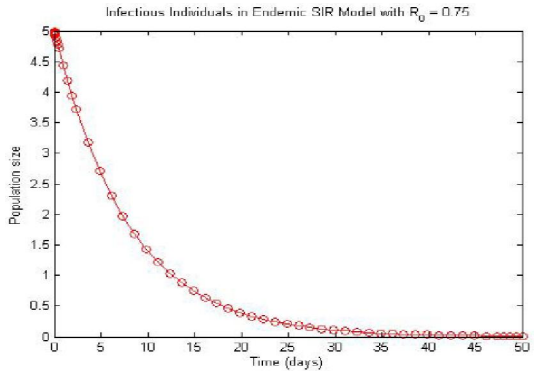

Figure 5(b) : Infectious individuals for the endemic model (2) with the basic reproductive number R_0 = 0.75.

sented in Figure 4(a) and the infectious population class is shown in Figure 4(b). Again we run the program taking the same parameters except β=*0.375* and the results are shown in Figure 5(a) and in Figure 5(b). From the figures, we it is easily understood that the behavior of the disease dynamics is quite different to that of model (1). However, here we only discuss the *standard incidence* case in this paper. Moreover, we do not include any control parameter to the dynamics of our discussed model. Our future research will focus on all such issues.

CONCLUSIONS

The periodic outbreaks of deadly nipah virus infections in Bangladesh have become the most public health concerns because of the highly mortality rates. Once an outbreak occurs in any region of Bangladesh, the virus can be transmitted to the whole family and/or even in the community, as Bangladesh is the most density populated (75% in rural areas) country in the world. So the ultimate demand is to the take immediate necessary steps

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so that the NiV infections can be ruled out completely. This paper focuses on the fundamental scenarios of NiV infections and the disease behavior by analyzing the dynamic model of the disease. A *SIR-type* model for the NiV infections has been formulated mathematically and then analyzed numerically. The analysis of the mathematical model and the simulation predictions clarify the mechanisms of the disease propagations and cell-virus interactions in the human body and thus suggest control strategies that could be implemented. Since proper drugs as well as effective vaccine are still not available for the treatments, this study may help the doctors and biologists to determining and obtaining control and preventive strategies from this deadly nipah virus infection.

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