Effect of the Seasonal Variation in the Extrinsic Incubation Period on the Long Term Behavior of the Dengue Hemorrhagic Fever Epidemic

Puntani Pongsumpun., and I-Ming Tang

Abstract—The incidences of dengue hemorrhagic disease (DHF) over the long term exhibit a seasonal behavior. It has been hypothesized that these behaviors are due to the seasonal climate changes which in turn induce a seasonal variation in the incubation period of the virus while it is developing the mosquito. The standard dynamic analysis is applied for analysis the Susceptible-Exposed-Infectious-Recovered (SEIR) model which includes an annual variation in the length of the extrinsic incubation period (EIP). The presence of both asymptomatic and symptomatic infections is allowed in the present model. We found that dynamic behavior of the endemic state changes as the influence of the seasonal variation of the EIP becomes stronger. As the influence is further increased, the trajectory exhibits sustained oscillations when it leaves the chaotic region.

Keywords—Chaotic behavior, dengue hemorrhagic fever, extrinsic incubation period, SEIR model.

I. INTRODUCTION

SURVEILLANCE of a variety of diseases has established that a regular seasonal variation in the incidences of the diseases is the rule, rather than the exception. Dowell [1] classifies the causes of seasonality into three categories; host-behavior changes, environmental changes and pathogen appearance and disappearance. One of the first seasonal variations to be observed was the rise and fall of measles deaths in London from 1703 onwards [2]. Environmental changes may lead to seasonal changes in the host physiology. Nelson and Drazen [3] found that the hormone, melatonin mediates a seasonal adjustment in the immune function. The melatonin secretion occurs nocturnally since the absence of light terminates the retina-mediated suppression of the pineal sympathetic activity and so the melatonin secretions are the highest in the late fall or winter seasons. Dowell et al. [4] pointed out that seasonal variation in the incidence of invasive pneumococcal disease correlates with the seasonal variation in the photoperiod (hours of darkness). For the arboviral disease, climatic factors are very important since the development of

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the mosquito and of the virus is affected by these factors. For instance, the temperature must be above 20^0 C, the threshold temperature below which the dengue virus can not reproduce in the mosquitoes [5]. Many people have also noted that the mosquito population increases drastically with the onset of heavy rainfalls. It has even been suggested that El Nino or La Nina may even be responsible [6] for the variation of some diseases. In this paper, we are interested in the effect of seasonality in the rain and temperature on the incidence of the dengue hemorrhagic disease.

Dowell [1], point out that the seasonal variations should be distinguished from periodic large epidemics as observed every two years for measles [7]. Explanation for the superannual cycle in the measles incidence rate is given in the study of Ferguson et al. [8] on the effects of a seasonal variation in the contact rate in a SEIR model for the transmission of measles. As one of the parameters in the seasonal varying contact rate is increased, the model begins to exhibit a complex bifurcation structure, with chaotic attractors and repellors in some regions of the parameter space. Ferguson et al. obtained a bifurcation plot containing chaotic bands that starts as a single limit cycle which undergoes period-doubling bifurcation leading to the next chaotic band. The period of the limit cycle is increased by one year after leaving each chaotic band.

It is the purpose of the present paper to study the transmission of dengue hemorrhagic fever (DHF) when there is a seasonal change in the length of the extrinsic incubation period (EIP) of the dengue virus when it is in the mosquito. As is known, the EIP becomes longer as the mean daily temperature is lowered. The temperature dependence of the incubation period τ versus T looks like a hyperbola with $\tau = 3$ days when the temperature is 32 ^{0}C and 14 days when it is 20 ^{0}C [9]. In Section II, we introduce the model and find two equilibrium states, a disease free state and an endemic state. We briefly review the stability conditions for the endemic state in Section III. In Section IV, we numerically solve the set of differential equations in the model using values of the parameters, which are biologically based. We obtain a bifurcation plot using the amplitude of the annual variation of the length of the EIP as the index parameter.

II. THE TRANSMISSION MODEL

To formulate a transmission model for dengue disease, one

needs to know what the disease is and what the transmission cycle is. Dengue hemorrhagic fever (DHF) is a more virulent form of dengue fever (DF), which is a rather benign febrile illness. DHF is characterized by the manifestation of plasma leakage, which if severe enough, leads to shock and possible to death. DF is an old disease, being mentioned in a Chinese encyclopedia published in the Chin Dynasty (265 to 420 AD). DHF first appeared in 1958 in the Philippines and since then, it has become the most important of the arboviral disease [10]. Both DF and DHF are caused by an infection by dengue virus (DV), of which there are four serotypes;DEN-1, DEN-2, DEN-3 and DEN-4. Infection by one DEN-serotype provides lifelong immunity to the infecting serotype.

Dengue hemorrhagic fever usually occurs when a person who has the antibodies to one serotype of the DV is infected by another serotype of the virus. According to the secondary infection hypothesis (or antibody-dependent enhancement hypothesis) [11], the preexisting heterogonous dengue virus antibody recognizes the infecting virus and forms an antigen-antibody complex. This complex attaches to the immunoglobulin Fc receptors on the cell membrane of the leukocytes. Because the antibody is heterogonous, it does not neutralize the new virus but instead allows it to invade the leukocyte. This virus is free to replicate itself within the cells. These infected cells, it is believed, produce and secrete vasoactive mediators, which causes in the vascular permeability, leading to increased plasma leakage.

The infection by any DV in the human begins when an infectious mosquito bites a human and injects a large number of the DV of one serotype into the blood of the human. There, the virus causes either a symptomatic or an asymptomatic infection in the person. The latter type of infections is more common than the former infection. Burke et al. [12] estimates that 87 % of dengue infections in one study in Thailand were either mild or asymptomatic. Within a year of an DEN-1 epidemic in Cuba in 1977 [13], 44.6 % of the population in Cuba had the antibodies to DEN-1 virus even though the reported number of confirmed DF illness in Cuba during the year was much less. The illness results from the former infection last for about one to two weeks. During this time, the infected person is immune to further infection by any of the four DV serotype. After the person recovers, he keeps his immunity to the infecting serotype but losses the temporary immunity he had to the other serotypes. If a susceptible mosquito bites a person while he has a high count of virus in his blood, the susceptible mosquito can become infected. It then takes from 3 to 14 days (the incubation period) for the virus to develop inside the mosquito before infectious, i.e., able to transmit the disease to a human by its bite.

Whether the epidemic can sustain itself and become endemic depends on a number called the basic reproduction number. It is the number of secondary infections, which can results from primary infection. Calling the number R, the disease will be self sustaining if R > 1 and will die out if R ≤ 1. This number can be determined as follows: If b is the biting rate (per day) of the mosquito and $I_v^{'}$ is the number of infected mosquitoes, then $b\,I_v^{'}$ is the total number of bites made by the infected mosquitoes each day. $\dfrac{S^{'}}{N_T + c}$ is the fraction of these bites which are delivered to susceptible humans (with S′ being the number of susceptible humans, c, number of other animals the mosquitoes can bite and N_T, the total number of humans). We multiply the product of the two terms by β_a and β_s, where β_a and β_s are the probability that the virus survives in the asymptomatic and symptomatic infectious humans, respectively. We have the number of bites by all mosquitoes that will result in new infections in the humans. Since some infected mosquitoes are not infectious (i.e. those in the EIP), they should not be included in the number $b\,I_v^{'}$. If a is the percentage of infected mosquitoes which are not infectious, then the number $a\,I_v^{'}$ should be subtracted from the total number of infected mosquitoes, leading the total number of infectious bites delivered to human and become asymptomatic infectious human to be $\left\{\dfrac{b\beta_a(1-a)}{N_T + c}\right\}S'I_v^{'}$. Similarly, $\left\{\dfrac{b\beta_s(1-a)}{N_T + c}\right\}S'I_v^{'}$ is the total number of infectious bites delivered to human and become symptomatic infectious human. We assume that the probabilities that the virus survives in the asymptomatic and symptomatic infectious humans are different. Setting c = 0, i.e., no other animals are present, these two terms become

$$b\beta_a(1-a)\left\{\dfrac{(A/\mu_v)}{N_T}\right\}S\,I_v \qquad \text{and} \qquad b\beta_s(1-a)\left\{\dfrac{(A/\mu_v)}{N_T}\right\}S\,I_v,$$

respectively, where S and I_v are the population densities.

$$b\beta_a(1-a)\left\{\dfrac{(A/\mu_v)}{N_T}\right\} \quad \text{and} \quad b\beta_s(1-a)\left\{\dfrac{(A/\mu_v)}{N_T}\right\} \quad \text{are the}$$

probability per day that the infection will be transmitted from a mosquito to a human and he becomes an asymptomatic and symptomatic infectious human, respectively.

Next, we note that $bS_v^{'}$ is the total number of bites that is made by susceptible mosquitoes ($S_v^{'}$ being the number of susceptible mosquitoes). $\dfrac{I'}{N_T + c}$ is the probability that these bites are made on infected humans (I′ being the number of infected humans). The product of these two when multiplied by β_v (the probability that the virus will survive in the mosquito after it is transmitted from the human) gives $b\beta_v I S_v^{'}$ as the number of bites by all mosquitoes that will lead to infectious in the mosquitoes. Dividing this by the total number of mosquitoes, we get for the probability that a bite by a mosquito on an infected human result in the mosquito becomes infected is $b\beta_v I S_v$. Multiplying the product of these two probabilities by the mean life times of the humans and

mosquitoes, we get the total number of secondary infections arising from a single primary infection, or basic reproduction number

$$R = \frac{b^2(\beta_a + \beta_s)m(1-a)}{\mu_v(\mu_h + r)} \qquad (1)$$

A. The Transmission Model

To describe the transmission of dengue disease, we formulate the mathematical model by dividing the human populations into four classes, susceptible, asymptomatic infectious, symptomatic infectious and recovered humans. We assume that both asymptomatic and symptomatic infectious humans can transmit dengue virus to the susceptible vector. The vector populations are separated into two classes, susceptible and infectious vector populations. The susceptible human (S') must already be carrying antibodies to one of the other serotypes of the DV. The antibodies may be the result of either symptomatic or asymptomatic infections. Asymptomatic and symptomatic infectious humans are the persons who are transmitted dengue virus from the infectious vector and can transmit dengue virus to the susceptible human. Recovered person is the infected person after the viremia stage until after they recover from dengue virus infection.

Let

$S'(t)$ denotes the number of susceptible human at time t,

$E'(t)$ denotes the number of asymptomatic infectious human at time t,

$I'(t)$ denotes the number of symptomatic infectious human at time t,

$R'(t)$ denotes the number of recovered human at time t,

$S_v'(t)$ denotes the number of susceptible vector population at time t,

$I_v'(t)$ denotes the number of infected vector population at time t.

The time rate of change in the number of subjects in each class is equal to the number of subjects entering into the group per unit time minus the number leaving the group per unit time. This gives

$$\frac{d}{dt}S' = \lambda N_T - \frac{b(\beta_a + \beta_s)}{N_T}(1-a)S'I_v' - \mu_h S', \qquad (2a)$$

$$\frac{d}{dt}E' = \frac{b\beta_a}{N_T}(1-a)S'I_v' - (\mu_h + r)E', \qquad (2b)$$

$$\frac{d}{dt}I' = \frac{b\beta_s}{N_T}(1-a)S'I_v' - (\mu_h + r)I', \qquad (2c)$$

$$\frac{d}{dt}R' = r(E'+I') - \mu_h R', \qquad (2d)$$

for the changes in the human population categories. In writing the above equation, we note that the susceptible humans become infected only if they are bitten by an infectious mosquito and not by an infected but not infectious mosquito.

$(1-a)I_v'$ is the number of infectious mosquitoes (see discussion at the end of previous section). For the mosquito population categories, we have

$$\frac{d}{dt}S_v' = A - \frac{b\beta_v}{N_T}S_v'(E'+I') - \mu_v S_v' \qquad (3a)$$

$$\text{and } \frac{d}{dt}I_v' = \frac{b\beta_v}{N_T}S_v'(E'+I') - \mu_v I_v' \qquad (3b)$$

In the equations above, A is the recruitment rate of female mosquitoes; $\mu_h(\mu_v)$, the death rate of the humans (mosquitoes); λ, the human birth rate and r is the rate at which the infected human recovers.

Dividing the human class by total human population and the mosquito classes by the total mosquito populations, we get the densities for each class. We also have $S + I + R = 1$ and $S_v + I_v = 1$ where the absence of the prime denotes a density. Because of these two constrains, only three equations are needed to define the model, i.e.,

$$\frac{d}{dt}S = \lambda - (\gamma_a + \gamma_s)SI_v - \mu_h S, \qquad (4a)$$

$$\frac{d}{dt}E = \gamma_a SI_v - (\mu_h + r)E, \qquad (4b)$$

$$\frac{d}{dt}I = \gamma_s SI_v - (\mu_h + r)I, \qquad (4c)$$

and

$$\frac{d}{dt}I_v = \gamma_v(1-I_v)(E+I) - \mu_v I_v \qquad (4d)$$

$$\text{where } \gamma_v = b\beta_v \qquad (5a)$$

$$\text{and } \gamma_a = b\beta_a m(1-a), \quad \gamma_s = b\beta_s m(1-a)$$

$$\text{with } m = \frac{(A/\mu_v)}{N_T} \qquad (5b)$$

B. Equilibrium States and Their Stabilitys

The equilibrium states are obtained by setting the RHS of eqns. (4a) to (4d) to zero. Doing this, we get two equilibrium states, the disease free state, $E_0' = (1, 0, 0, 0)$ and the endemic equilibrium state, $E_1 = (S^*, E^*, I^*, I_v^*)$

$$\text{where } S^* = \frac{\beta + M}{\beta + MR}, \qquad (6a)$$

$$E^* = \frac{R_a}{R}\frac{(R-1)}{(\beta + MR)}, \qquad (6b)$$

$$I^* = \frac{R_s}{R}\frac{(R-1)}{(\beta + MR)}, \qquad (6c)$$

$$I_v^* = \frac{\beta}{R}\frac{(R-1)}{(\beta + M)} \qquad (6d)$$

$$\text{where } \beta = \frac{b\beta_v}{\mu_v}, \quad M = \frac{\mu_h + r}{\mu_h},$$

$$R_a = \frac{b^2\beta_a\beta_v m(1-a)}{\mu_v(\mu_h + r)}, \quad R_s = \frac{b^2\beta_s\beta_v m(1-a)}{\mu_v(\mu_h + r)}$$

and

$$R = \frac{b^2(\beta_a + \beta_s)\beta_v m(1-a)}{\mu_v(\mu_h + r)} \qquad (6e)$$

The local stability of an equilibrium state is determined from the Jacobian (gradient) matrix of the RHS of equations (4a)-(4d) evaluated at the equilibrium state. If all eigenvalues (obtained by diagonalizing the Jacobian matrix) have negative real parts, then the equilibrium state is locally asymptotically stable. Diagonalizing the Jacobian for the endemic equilibrium state, we find that the characteristic equation is;

$$(\lambda + M\mu_h)(\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0) = 0 \qquad (7)$$

where

$$a_2 = \frac{(\beta + M(M + R + \beta))\mu_h}{M + \beta} + \frac{R(M + \beta)\mu_v}{MR + \beta}$$

$$a_1 = \frac{M(MR + \beta)\mu_h^2}{M + \beta} + \frac{(R\beta + M(R^2 + (R-1)\beta))\mu_h\mu_v}{MR + \beta}$$

$$a_0 = M(R - 1)\mu_h^2\mu_v \qquad (8)$$

It can be seen that one eigenvalue has negative real part. The other eigenvalues have negative real part if it satisfies the Routh-Hurwitz criteria [14], that is

$$a_2 > 0, a_1 > 0 \text{ and } a_2 a_1 > a_0 \qquad (9)$$

It can be demonstrated that the coefficients a_2, a_1 and a_0 satisfy (9) for R > 1. Therefore the endemic equilibrium state would be local asymptotically stable if R > 1.

III. NUMERICAL CALCULATIONS

We are interested in the transmission of diseases, we should only be interested in whether a person is infectious or not and is immune or not, not whether he is sick. The susceptible class is made up of people who have no immunity and are not infectious. A person infected with the dengue virus is only infectious during the viremia period, which lasts around three days. After that, the person remains sick for one or two weeks. Once the person becomes well, he enters into the recovery class with life long immunity to the virus. While the person is infected with the virus, he also has immunity to further infection by a new virus. Accordingly, a recovered person is the same as an infected person after the viremia period. Since the viremia period last three days [15], the recovery rate should be equal to 1/3 per day and not the inverse of the length of the illness.

The values of most of the other parameters are determined by the real life observations. They are $\mu_h = 0.0000456$ per day, corresponding to a life expectancy of 60 years; $\mu_v = 0.071$ per day, corresponding to a mosquito mean life of 14 days; b = 0.33, one bite providing enough blood meal for three days; $\beta_a = 0.3$, $\beta_s = 0.2$ and $\beta_v = 0.75$, which were chosen arbitrarily. The ratio m can be adjusted to give a desired value of R. Setting m to be 2 and ignoring the effect of the time delay

(EIP), we find that R = 3.50. The equilibrium state would be the endemic equilibrium state (0.290247, 0.000058, 0.0000387, 0.000337) and according to the conditions established in the previous section, it would be a stable spiral node. Looking at fig. 1, we see that the trajectory in the S-E and S-I phase space are spiraling into the endemic equilibrium state. In fig.2, we find that the time evolutions of asymptomatic and symptomatic infectious human population exhibit a damped oscillation with a period of 7 years when it approaches the endemic equilibrium point. If we adjust the parameters (i.e., change m to 10) so that R = 17, the period of oscillation is reduced to 2.6 years. We have plotted on fig.3, the time evolution of the asymptomatic and symptomatic infectious human population when the new set of values is used.
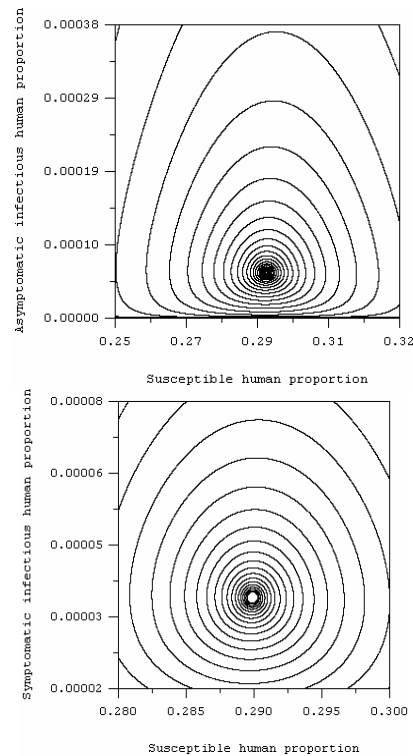

Fig. 1 Spiral Trajectory in the Susceptible-Asymptomatic Plane and Susceptible-Symptomatic Plane. Using the numerical values given in the text, the trajectory spiral into the equilibrium state $(S^*, E^*) = (0.290247, 0.000058)$ and $(S^*, I^*) = (0.290247, 0.0000387)$, respectively because the values of the parameters satisfy the Routh-Hurwitz.
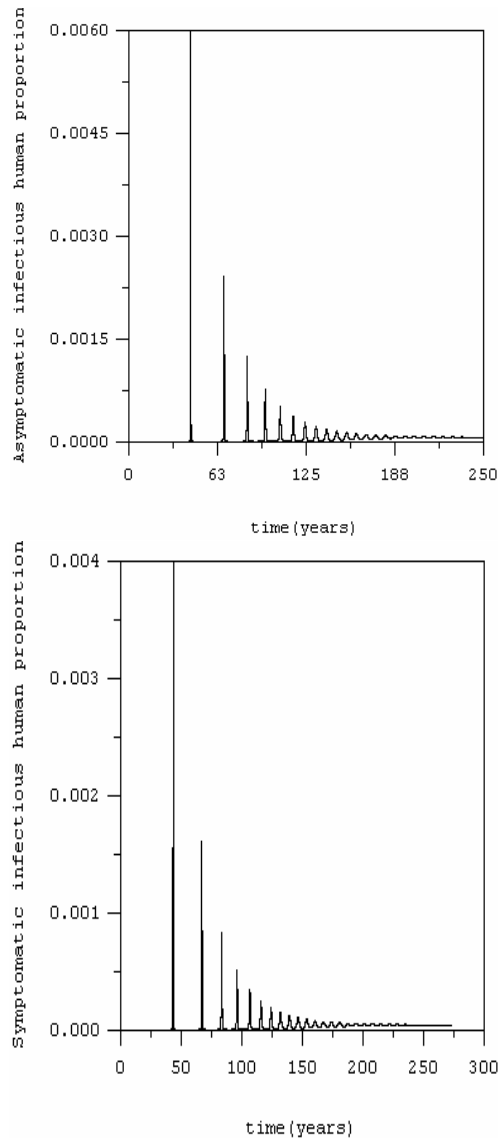
Fig. 2 Time Evolutions of asymptomatic and symptomatic infectious human population. The period of oscillation is about 7 years.

Fig. 3 Time evolution of the infected human for a new set of values for the parameters. The change in time evolution of the infected population when R = 17. The period of oscillation is reduced to 2.6 years.

In general, small R's result in long periods while large R's result in short periods. A similar trend was seen in a study of the transmission of *Plasmodium falciparum* based on a SEIS model of transmission [16]. In that study, the period of the damped oscillation predicted by the model dropped from about 40 years to about 20 years when the set of parameter values which yielded a value R equal 1.3 was changed to the set of values which yielded a value of 3.34. For our model to generate oscillation of one-year period, the value of R would have to be much greater than the values observed in nature. In the next section, we will show by including a seasonal variation in one of the probability factors, both the annual and multiple year cycles can be predicted.
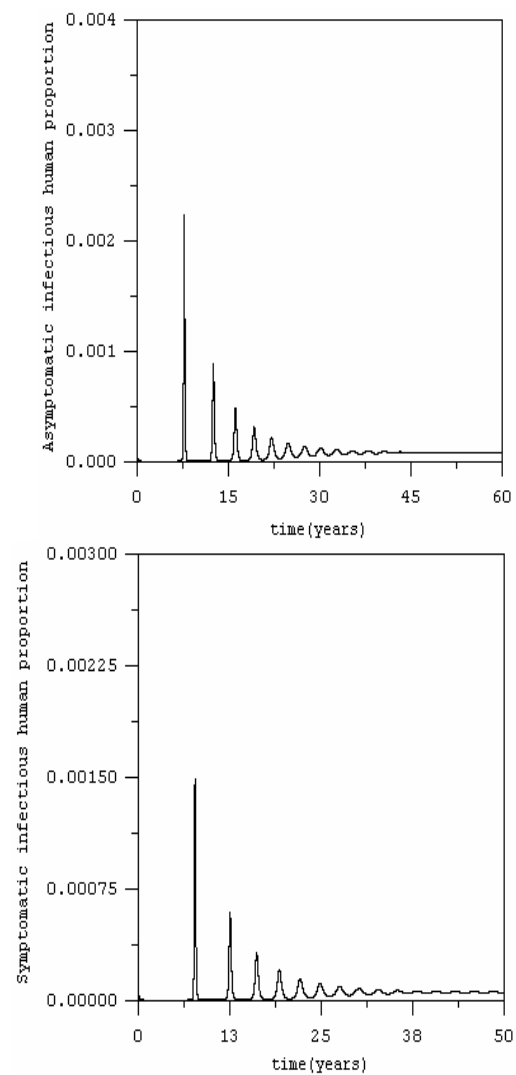
IV. SEASONALITY IN THE INCIDENCE OF DENGUE HEMORRHAGIC FEVER

It was suggested long time ago, [17] that the variation in the extrinsic incubation period (EIP) caused by changes in the (lowest daily) temperature changes was the cause of the seasonality in the transmission of dengue disease. In this study, the EIP enters into the model through the dependence of 'a' (the fraction of the infected mosquitoes existing in the EIP) on τ. The fraction is given by

$$a = \int_0^{\tau} e^{-\mu_v t} dt$$

$$= \frac{1 - e^{-\mu_v \tau}}{\mu_v}$$

(10)

where τ is the length of latent or incubation period.

Substituting these revised probabilities $\beta'_a = \beta_a(1\text{-}a)$ and $\beta'_s = \beta_s(1\text{-}a)$ and then expanding the exponential, we get

$$\beta'_a \quad = \quad \beta_a\left(1+\tau\left(1-\frac{\mu_v\tau}{2}+O\left((\mu_v\tau)^2\right)\right)\right) \tag{11}$$

and

$$\beta'_s \quad = \quad \beta_s\left(1+\tau\left(1-\frac{\mu_v\tau}{2}+O\left((\mu_v\tau)^2\right)\right)\right) \tag{12}$$

As we have already point out, the dependences of β'_a and β'_s on T arise because the dependence of the latent period depends on T. Though the dependence looks like a hyperbola, with $\tau = 3$ days at 32^0C and 14 days at 20^0C, we have modeled the variation as a sinusoidal variation, i.e.,

$$\beta'_a \quad = \quad \beta_a(1+\delta\sin\omega t) \tag{13}$$

and

$$\beta'_s \quad = \quad \beta_s(1+\delta\sin\omega t) \tag{14}$$

where δ is a measure of the influence of the seasonality on the transmission process.

Depending on the values of δ and the other parameters, the basic reproduction number could remain above R = 1 throughout the year or it could drop below 1 during part of the year, resulting in some complicated behaviors. To see what could happen, we have plotted on fig.4, a bifurcation plot using δ as an index parameter. We see in fig. 4, the first period doubling bifurcation at $\delta = 0.24$, the second at 0.62, the third at 0.77. At $\delta = 0.8$, a chaotic band appears. As δ is further increased, a non-chaotic interval appears at $\delta = 0.88$ and enters into another chaotic band as δ is increased to 0.92. We have changed some values, which were used to get the curves in fig.1. The changed values are m = 11, $\mu_v = 1/17$, $\beta_v = 1.0$, $\beta_a = 0.5$ and $\beta_s = 0.5$. These and the other values used yield a $R_0 = 45$. In fig.5, we plot the time evolution of the asymptomatic and symptomatic infectious human population after a long passage of time. We observe that the chaotic behavior occur as the time is passed.
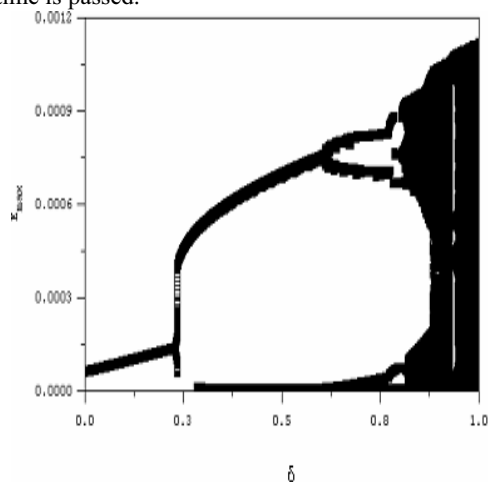

Fig. 4 Bifurcation diagram showing the maximum value of E and I for the range of values of the index parameter δ. The top frame is a plot of E while the lower frame is for I. The values of the parameters are given in the text. We see a series of period doubling bifurcation occurring at $\delta = 0.24$, 0.62 and 0.77. When δ reaches 0.80, a bifurcation into a chaotic band occurs. A non-chaotic band emerges at $\delta = 0.88$ and a new chaotic band appears as δ is increased to 0.92.
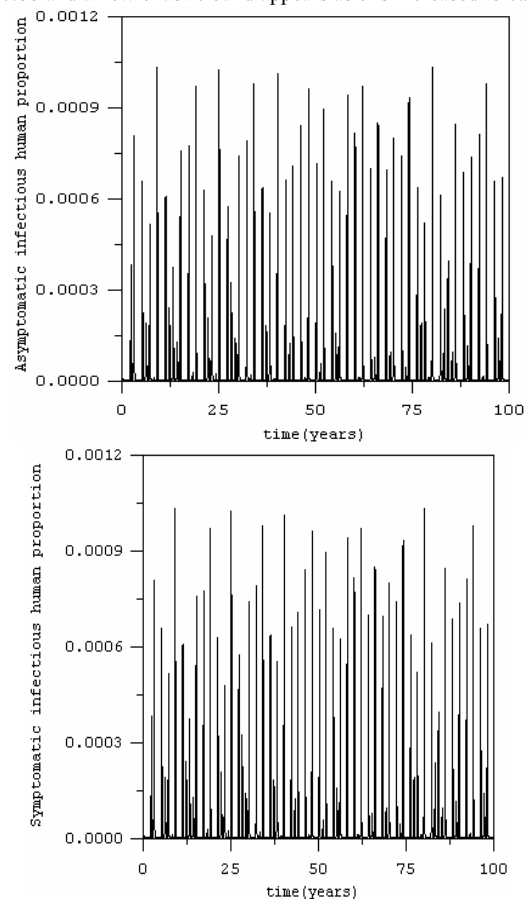

Fig. 5 Long time incidence rate where a seasonal variation in the EIP occurs. The values of the parameters are given in the text. The value of the index parameter δ is set at 0.90, a value putting E_{max} and I_{max} in

the non-chaotic band emerging from the first chaotic band.

V. DISCUSSION

The generation of chaotic behavior by a seasonally forcing term should not be surprising. In addition to Ferguson *et al.* [8] study on measles, Olsen *et al.*, [18] have also noted the possibility of oscillations and chaos in six childhood diseases in Copenhagen, Denmark. Recently, Gakkhar and Naji [19] have studied the effects of seasonality on a prey-predator model where in the absence of the seasonality, the system has a globally stable limit cycle. They detected an abundance of steady state chaotic solutions. Their results support the conjecture that seasons can give rise to complex population dynamics. In a later study, [20] they considered the cases where the seasonality appears in two places in their model. They obtained extremely rich bifurcation diagrams, which showed long periodic regions emerging from chaotic bands as various parameters in their predator-dependent functional response term in a Lotka-Volterra like model of a predator-prey system. In present study, the seasonality appears in one place.

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