Original Article

A dengue transmission model in Thailand considering sequential infections with all four serotypes

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Abstract

Background: Dengue fever/dengue haemorrhagic fever is prevalent in Thailand, where all serotypes are found and the dominant serotype has changed irregularly. Although almost all primary infections present with slight symptoms or are asymptomatic, little is known about the infectiousness of dengue fever.

Methodology: A mathematical model of the transmission for dengue virus was constructed covering the possibility of sequential infections with all four different serotypes. The model was combined with the seasonal population dynamics of *Aedes aegypti*, the principal vectors of dengue virus in Thailand. The contributions of inapparent cases in the transmission to mosquito vectors and antibody-dependent enhancement were incorporated into the model. Moreover, the hypothesis of an "unnatural" infection route was examined, where a person acquires immunity by infection during a cross-immunity period, through model simulations.

Results: A comparative study on the transmission probabilities of inapparent cases to mosquito vectors showed that the prevalence of dengue infection could be immediately stamped out after a severe outbreak if inapparent cases had no infectiousness. The simulation under an "unnatural" infection route assumption resulted of yearly changes in the dominant serotype and sharp, irregular variations in outbreaks.

Conclusion: The supposition that inapparent cases had no infectiousness was not in accord with the actual situation in Thailand. Furthermore, the simulation result supported the "unnatural" infection route as having an influence on epidemics of dengue.

Key words: dengue, inapparent infection, Thailand, antibody-dependent-enhancement, mathematical model

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Introduction

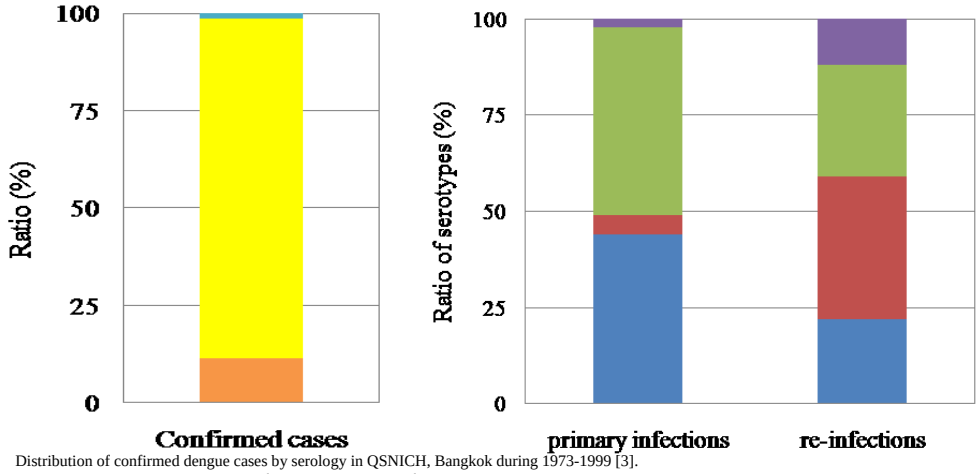
Dengue infection (dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)), which is caused by dengue virus (DENV), is an endemic disease with a low mortality rate in southeastern Asian countries. Because most infections in this area occur in Thailand, DF/DHF is a serious disease in this country [1,2]. In Thailand, serotypes 1-4 of DENV are widespread [3]. Most cases are infected with dengue in childhood, so a significant proportion of children have obtained immunity to all serotypes [4]. In Thailand, dengue epidemics have occurred every year in the last 40 years. The incidence was recorded as 325 per 100,000 when an outbreak of DF occurred in 1987 [3]. Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok diagnosed 15,376 dengue infection patients during 1973-1999. It was observed that all four serotypes were found, and that the dominant serotype, which accounted for the most patients among the four serotypes, changed irregularly [3].

Frequently, the statistics on dengue patients are gathered in reports from regional health management organizations. In Thailand, clinically diagnosed cases of DF, DHF and DSS are regularly reported to the Provincial Health Offices [5,6]. The total number of infected persons remains unknown without active detection surveillance because slight or asymptomatic persons rarely visit a hospital for treatment [7].

In this article, a mathematical model of the transmission for dengue virus was constructed covering the possibility of sequential infections with all four different serotypes to investigate how inapparent cases affect the prevalence of dengue infection, to estimate the incidence of DF/DHF including inapparent cases, and to study the succession of the dominant serotype. *Aedes aegypti* was recognized as the principle vector of DENV in Thailand [8-10]. The model of dengue transmission was combined with the seasonal population dynamics of *A. aegypti*.

There are many susceptible-infected-recovered (SIR)-transmission models of various infectious

Figure 1.



Distribution of confirmed dengue cases by serology in QSNICH, Bangkok during 1973-1999 [3].
(a) Distinction between the primary infections (orange), re-infections (yellow) and unknown (sky-blue).
(b) Distributions of isolated serotypes in patients with primary infections and re-infections. Each serotype is denoted by a different color (Den-1, blue; Den-2, red; Den-3, green; and Den-4, purple)

diseases, including DF. Derouich [11] studied the maintenance in a dengue epidemic with two serotypes by a basic SIR model. Bartley [12] developed a two-serotype dengue transmission model in consideration of the seasonal population dynamics of *A. aegypti*. Wearing [13] constructed a four-serotype model for DF in Thailand considering the influence of antibody-dependent enhancement (ADE). The present model incorporates seasonal variations in the population of *A. aegypti*, inapparent cases that influence prevalence, and the influence of ADE. The epidemiological parameters were estimated from investigations in Kamphaeng Phet Province [1,14,15] to improve the model realistically.

Comparative studies on transmission probabilities of inapparent cases to mosquito vectors showed that the prevalence of dengue infection could be immediately stamped out after a severe outbreak if inapparent cases had no infectiousness, which was not in accord with the actual situation in Thailand. Moreover, an examination was made of an "unnatural" infection route of dengue transmission [16] that Nagao and Koelle [17] adopted in their transmission model. The assumption of an "unnatural" infection route means that a person during a cross-immunity period can be asymptomatically infected with another serotype than the serotypes they have acquired immunity to. The simulation showed the "unnatural" infection route assumption occurred with a clear change of the dominant serotype and with sharp and irregular variation in outbreaks, while the dominant serotype changed in a steady regular rotation without the "unnatural" infection route assumption.

Materials and methods

Available data

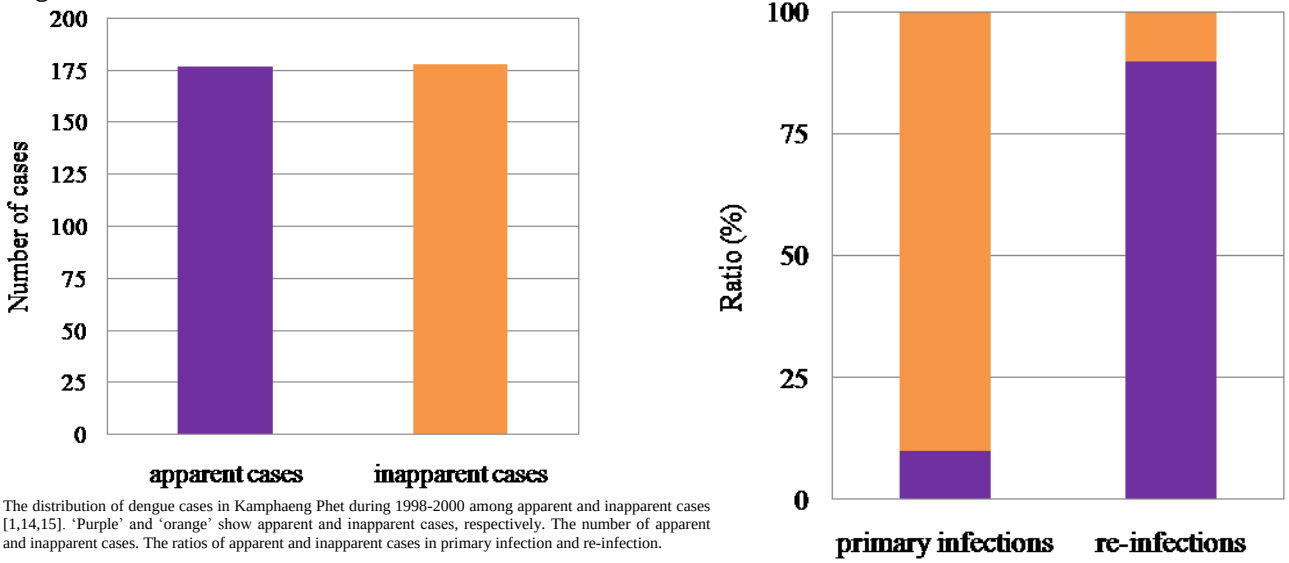
The report on dengue patients under 18 years old at QSNICH, Bangkok, during 1973-1999 contained the detection of the serotype of DENV by blood serum analysis of patients in acute or convalescent phases, the differential diagnosis of primary DF and DHF/DSS, and the distinction between primary infection and re-infection. The report stated that 87% of patients were classified as re-infection, and the distribution of serotypes in patients in primary and re-infection cases [3] (Figure1).

Active detection surveillance of dengue infection was performed for about 2,000 students in 12 primary schools in Kamphaeng Phet province in northern Thailand during 1998-2002 [1,14,15]. In the study, all students absent due to illness were diagnosed as DF or not. In addition, students in good health were checked for their height and weight, and a blood sample for dengue serology was taken three times during each surveillance period (June 1-August 15, August 16-November 15) in the dengue season. It was reported that the incidence of apparent and inapparent cases were estimated as 4.3%, 3.6% (1998), 3.2%, 3.3% (1999), and 1.4%, 0.8% (2000), respectively (Figure 2).

The transition of infection stage (in humans)

Persons who are bitten by an infected mosquito develop DF after the incubation period ($1/\sigma_H$) of 2-12 days [16], 5.7 (DEN-1), 6.0 (DEN-4) days [18]. However, most persons infected for the first time are asymptomatic, while most re-infected persons develop apparent symptoms [14]; therefore, infected

Figure 2.



The distribution of dengue cases in Kamphaeng Phet during 1998-2000 among apparent and inapparent cases [1,14,15]. 'Purple' and 'orange' show apparent and inapparent cases, respectively. The number of apparent and inapparent cases. The ratios of apparent and inapparent cases in primary infection and re-infection.

states were distinguished between apparent and inapparent infections. In apparent cases, symptoms last for two to seven days (the infectious period, $1/\gamma_H$) [19,20]. Recently, it was reported that three cases of simultaneous infections with multiple serotypes were detected in Thailand [21]; however, the model was limited to a single serotype infection at a time. The model also assumed that immunity to re-infection with a previously experienced serotype holds lifelong, which was consistent with experimental data [22]. A temporary cross-immunity with other serotypes occurs after recovery and lasts for two to nine months [16,22,23]. ADE, which is a negative immune reaction, occurs after the temporal cross-immunity period [13,24]. ADE may increase the risk of progression to DHF and the transmission probabilities of DENV from vector to human and also from human to vector. $\beta_{H(i)}$ stands for the transmission probability from a vector infected with *i*-serotype DENV to human. To reflect the influence of ADE in the model, the transmission probability for re-infection with *i*-serotype is represented as the product of $\beta_{H(i)}$ by the enhancement multiple $\chi_{(i)}$. An increase of DHF-development risk by ADE is represented as a boost in the ratio of apparent symptoms in patients in the model because of the lack of a distinction between DHF and DF. $\beta_{V(i)}$ stands for the transmission probability from a person infected with *i*-serotype DENV to a vector. There was little information about the infectiousness of inapparent cases. It was reported that DHF patients showed peak viremia levels 100-1,000 times higher than DF patients, which suggests the relation of infectiousness to the severity of symptoms [25]. As the amount of DENV particles in an inapparent case is assumed to be less than that in an apparent case, the infectiousness of inapparent cases should be lower than that of apparent cases. So, the transmission probability from an inapparent case to a vector is represented as the product of $\beta_{V(i)}$ and a reduction weight (y (0.0-1.0)).

Estimates of transmission probability

According to the report of QSNICH [3], DEN-3 was the most frequent isolate (49%), followed by DEN-1 (44%), DEN-2 (5%), DEN-4 (2%) in primary infections, and DEN-2 was the most frequent isolate (37%) and followed by DEN-3 (29%), DEN-1 (22%), DEN-4 (12%) in re-infection cases. The transmission rate for each serotype ($\beta_{H(i)}$) in primary infections was arranged by size in order of DEN-3, DEN-1, DEN-2, and DEN-4, which were fixed by the product of the multiplier and β, when the transmission rate of DEN-4 (β) was chosen as the standard. The transmission rate for each serotype in re-infection cases was given by the product of the enhancement multiple ($\chi_{(i)}$) and $\beta_{H(i)}$, then the order by size as follows: DEN-2, DEN-3, DEN-1, and DEN-4. For re-infection, the value of $\chi_{(3)}\beta_{H(3)}$ was larger than that of the other serotypes in contrast to the order above. Because most people are infected with DEN-3 in primary infections, a significant number of persons have obtained immunity to DEN-3 and a few persons can be infected with DEN-3 in re-infection cases. The influence of ADE in third and fourth infections was still unknown, but the risk for DHF with the third and

Table 1. Transmission probability from vector and enhancement multiples by serotype.

Serotype(i)	Transmission probability from vector infected by i-serotype $\beta_{H(i)}$	Enhancement multiple $\chi_{(i)}$
1	1.4β	1.0
2	1.1β	1.3
3	1.5β	1.1
4	β	1.1

fourth infection was not different from that with the second infection in QSNICH [26]. The influence of ADE in third and fourth infections was assumed to be equal to the second infection. Then, the multipliers in $\beta_{H(i)}$ and $\chi_{(i)}$ were chosen as satisfying the observed orders of isolated serotypes in both primary infection and re-infection cases [3] (Table 1).

According to the surveillance in Kamphaeng Phet province [1,15], there were 154 students with symptoms and 177 students with no symptoms of about 2,000 primary school students during the investigation period over three years. The incidence per year was assumed to be 110/2,000 in the schoolchildren age category and the incidences of apparent and inapparent cases were assumed to be equal. Then, we set $\beta = 0.35$ and $x_1 = 0.1$, $x_2 = x_3 = x_4 = 0.5$ (Table 2). The transmission rates for all serotypes from human to mosquito were assumed to be equal and were set at $\beta_{V(1)} = \beta_{V(2)} = \beta_{V(3)} = \beta_{V(4)} = 0.3$ (Table 2).

Population dynamics of mosquito vectors

The principal vector of DENV in Thailand is *A. aegypti* [9,27]. In Thailand, temperatures are maintained at a level suitable for breeding of *A. aegypti* throughout the year, which is the reason DF prevails in all seasons [28]. The population of *A. aegypti* varies by season. A survey of *A. aegypti* in Chachoengsao province in Thailand, which is located 100 km east of Bangkok and has a similar climate to Bangkok, showed that the number of larvae of *A. aegypti* in the wet season was more than that in the hot and cool seasons, and that in the hot season was greater than in the cool season [9,10]. The life expectancy of *A. aegypti* ($1/\mu_V$) was estimated as 14 days [29]. A model of the population dynamics of *A. aegypti* was constructed. The wet season is divided into two parts by the level of rainfall; therefore, the model had four seasons: February-April as the hot season, May-July as the wet season *1*, August-October as wet season *2*, and November-January as the cool season. The emergence rate of *A. aegypti* (μ_V') was estimated from the above survey [9,10] (Table 3).

Mathematical model

Population dynamics by age

In Thailand, cases of dengue infection are frequently infected in childhood. The susceptibility and the seriousness of dengue infection seem to vary by age [30]. Therefore, the total population was classified into five age categories from school age, which were represented by Nh^a ($a = 1, \ldots, 5$).

The average lifespans of men and women in Thailand in 2006 were 69 and 75 years, respectively [31]. The model assumed that the average lifespan was 70 years and the death rate (μ_H) was 1/70 (year^{-1}) and that the population of every category and also the total population held stable ($Nh^a/dt = 0$), which led to the determination of the birth rate being equal to the death rate (μ_H) and the transfer rates from Nh^a to Nh^{a+1} (Table 4).

Model scheme without an "unnatural" infection route assumption

The effect of an "unnatural" infection route assumption was investigated on the dengue epidemic, where a person during the cross-immunity period can be infected, which was adopted in the model by Nagao and Koelle [17]. When the "unnatural" infection route assumption was not adopted, the total population was divided into five epidemiological classes that each contained five age categories: a susceptible class that could be infected by any of the serotypes except for the serotypes that it had already acquired immunity for; an exposed class that had been bitten by an infected mosquito but had not yet reached infectivity; an apparently infected class that had infectivity with symptoms; an inapparently infected class that had infectivity without symptoms; and a cross-immunity class that had immunity to all four serotypes just after recovery. The above epidemiological classes were superscripted to *Sh*, *Eh*, *Ih*, *Ih'*, *Ch* with age categories and the serotypes' current infection and those that had already obtained immunity were subscripted. The model scheme of the primary infection of dengue with the epidemiological classes and the transfers among them are shown in Figure 3. As a person may be infected four times with the four serotypes, the model could allow up to four

Table 2. Estimated parameter values in simulation.

Symbol		Description	Estimated value
	μ_H	Human birth rate ＝death rate	1/70 year^{-1}
	$\beta_{H(i)}$	Transmission probability from vector infected with *i*-serotype dengue virus to human	See Table 1
	β	$\beta_{H(4)}$	0.35
	$\chi_{(i)}$	Enhancement multiple for the i -serotype	See Table 1
x_m	x_1	Ratio of apparent symptom	0.1
	x_2,x_3,x_4	patients in the *m*-th infection	0.5
	$1/\sigma_H$	Incubation period in humans	5 days
	$1/\gamma_H$	Infectious period in humans	6 days
	$1/\delta_H$	Cross-immunity period in humans	3 months
	μ_V'	Mosquito emergence rate	See Table 3
	μ_V	Mosquito death rate	1/14 day^{-1}
	$\beta_{V(i)}$	Transmission probability from host infected i -serotype dengue virus to vector	0.3
	$1/\sigma_V$	Incubation period in mosquitoes	10 days
	b	Human biting rate	1/2 day^{-1}

Figure 3. Model scheme of dengue in primary infections in humans.

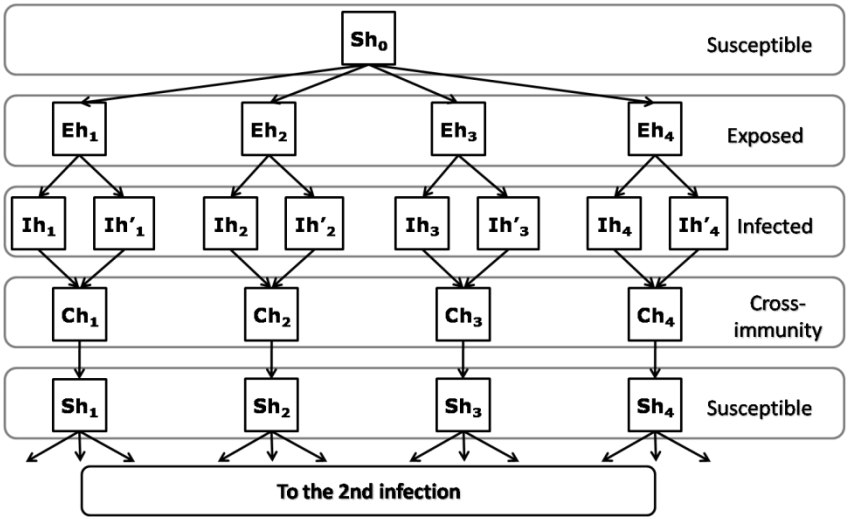


Table 3. Estimated emergence rate of mosquitoes.

Season	Emergence rate μ_V' (day^{-1})
February-April (hot season)	1/15
May-July (wet season 1)	1/13.5
August-October (wet season 2)	1/12.4
November-January (cool season)	1/15.5

Table 4. Age categories and the transfer rates among age categories.

Symbol	Age category (years)	Transfer rate f^a (day^{-1})	Population
Nh^1	-6	0.443×10^{-3}	2179.0
Nh^2	7-12	0.443×10^{-3}	2000.0
Nh^3	13-20	0.328×10^{-3}	2413.5
Nh^4	21-50	0.074×10^{-3}	6948.3
Nh^5	51-	---	12985.9
Total			26526.6

infections with different serotypes, where the model scheme of the second, third, and fourth infections was similar to the primary one.

Model scheme with an "unnatural" infection route assumption

When an "unnatural" infection route assumption was adopted, the new exposed class (*Eh'*) was added to the previous model. If a person is infected with a serotype other than the serotypes that he or she had acquired immunity to during the cross-immunity period, the patient moves to the newly exposed class *Eh'* and thereafter to the inapparently infected class (*Ih'*) because he or she is probably asymptomatic or shows slight symptoms due to the effect of cross-immunity (Figure 4).

Model scheme in mosquitoes

The total mosquito population (*Nv*) was divided into three epidemiological classes: a susceptible class, an exposed class, and an infected class, which were represented by *Sv*, *Ev* and *Iv*, respectively. An infected mosquito has infectiousness for its lifetime. The model was limited to a single serotype infection (Figure 5). Pepin *et al*. [32] reported that competition between serotypes could affect virus titers in multiple infections in mosquitoes, which suggested that the transmission probability was decreased.

Results

The progress of a dengue epidemic was simulated using a transmission model. The simulations postulated that the population of mosquitoes, which vary seasonally, followed emergence rates in the four seasons, comprising 300,000 on every January 1st (Figure 6) and that the human population was set as about 26,500 to give a second age category (7-12 years) of 2,000 in accordance with the number of schoolchildren in Kamphaeng Phet province (Table 4). The results of simulations for 10 years were obtained after a burn-in period of 10 years by introducing four persons who were infected with the different serotypes into all negative populations.

Comparison among situations with and without an "unnatural" infection route assumption

The numbers of apparent and inapparent cases in the total population and in the schoolchildren age category (7-12 years) were observed under situations with and without an "unnatural" infection route assumption. The reduction weight of the transmission probability in the inapparently infected class (y) was assumed to be reduced to 50% of that in the apparently infected class (y = 0.5) because an inapparent case had lower infectiousness than an apparent case. The numbers of apparent and inapparent cases changed seasonally according to the dynamics of mosquito vectors. The dominant serotype changed in a steady rotation without the "unnatural" infection route assumption, while it changed irregularly with an "unnatural" infection route assumption (Figure 7). Comparison of the number of apparent cases in two age group categories,

Figure 4. Model scheme with the "unnatural" infection route assumption in humans.

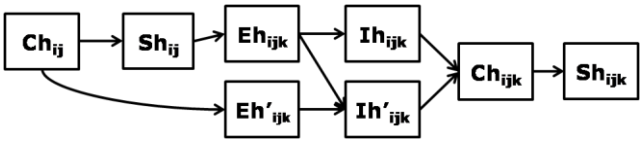


Figure 5. Model scheme of dengue in vectors.

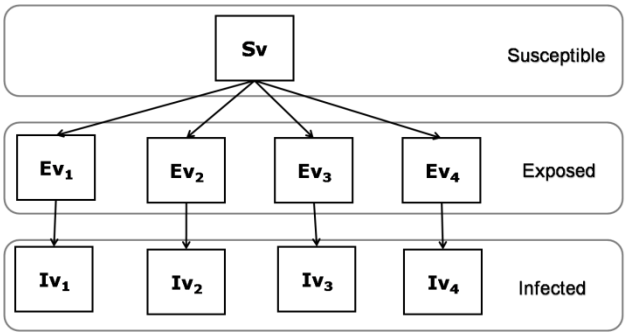
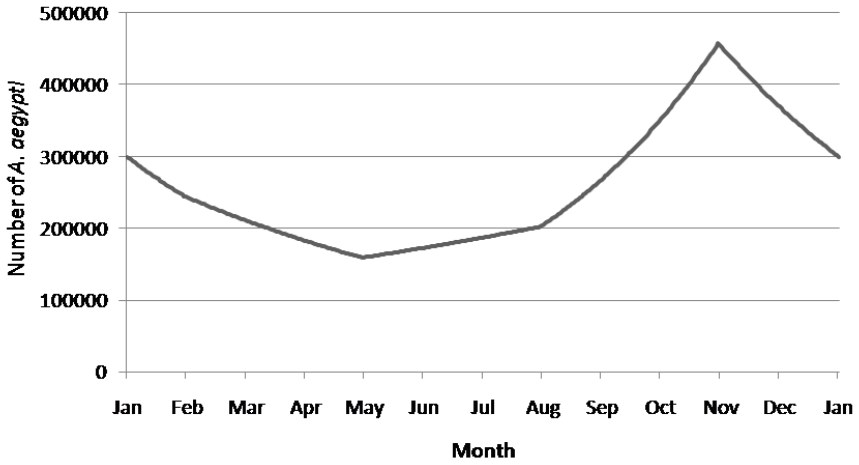


Figure 6. Seasonal profile of the *A. aegypti* population.



schoolchildren and older, among situations with and without an "unnatural" infection route assumption are shown in Figure 8.

Comparison among reduction weights of transmission probability in the inapparently infected class

For the situation that inapparent cases were assumed to have no infectiousness (y = 0.0), a major epidemic broke out once, but it took a long time until the next epidemic occurred without the "unnatural" infection route assumption, while DF was eliminated after a major outbreak because almost all persons gained immunity to all four serotypes rapidly with the "unnatural" infection route assumption (Figure 9).

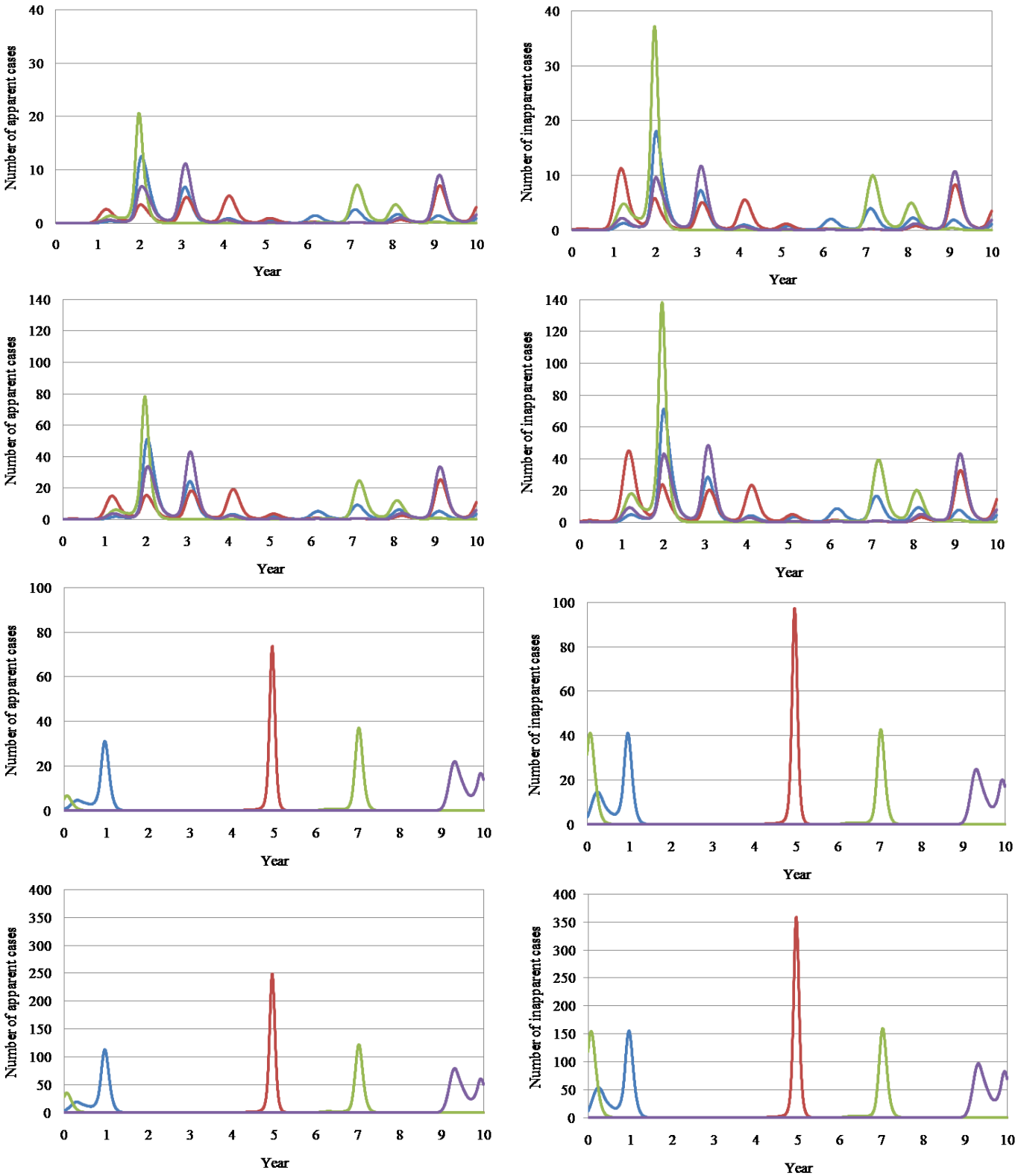
Sensitivity for the incidence to variations in the transmission probability parameter values

The sensitivity for the incidences of both apparent and inapparent dengue cases to variations in the values of the transmission probabilities from vector to human (β), from human to vector (β_V), and the reduction weight of the transmission probability in inapparent cases (y) were examined through simulations for 10 years. Figure 10 shows the relative incidences for these parameter values with a range of 0.15 around the adopted values (β = 0.35, β_V = 0.3, y = 0.5) in the model under situations without and with the "unnatural" infection route assumption. Mild fluctuations in the incidences of both apparent and inapparent cases were found when the value of the transmission probabilities holds the above-adopted value or over. On the other hand, the incidence decreases when the value tends towards zero.

Discussion

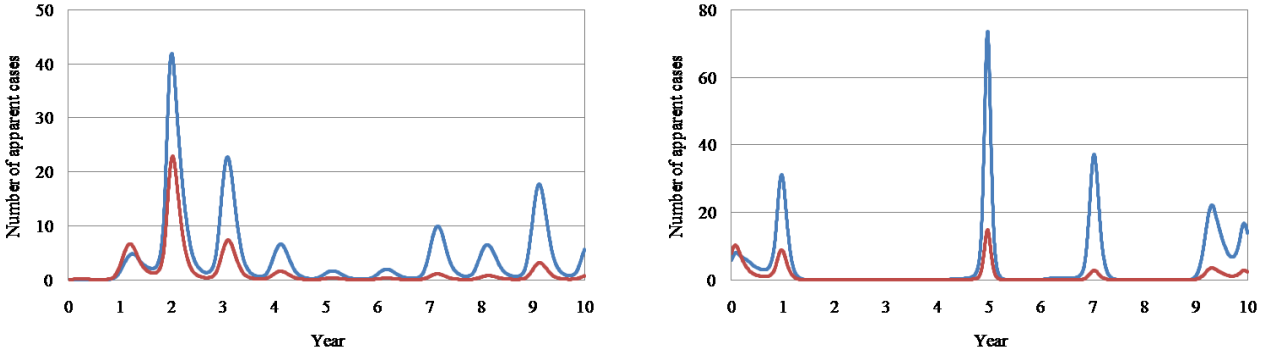
The report on DF by QSNICH indicated that only 11% of patients were primary infections and that other 87% were re-infection cases [3]. The surveillance of DF in Kamphaeng Phet also showed

Figure 7.



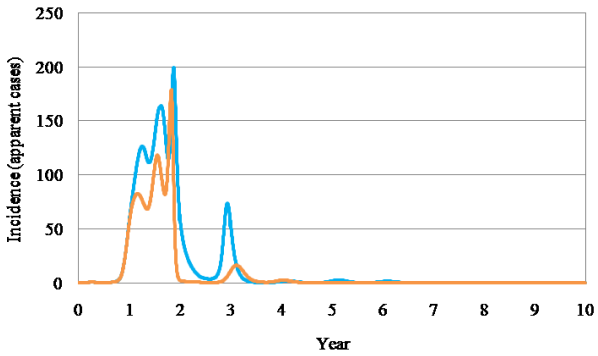
The transition of inapparent and apparent cases for 4-serotypes in the situation of $y = 0.5$ without (a-d) and with (e-h) the "unnatural" infection route assumption. (a, b, e, f), (c, d, g, h) show the second age category (7-12 years) and the sum of all age categories, respectively. (a, c, e, g) and (b, d, f, h) show apparent and inapparent cases. Each serotype is denoted by a different color (Den-1, blue; Den-2, red; Den-3, green; and Den-4, purple).

Figure 8



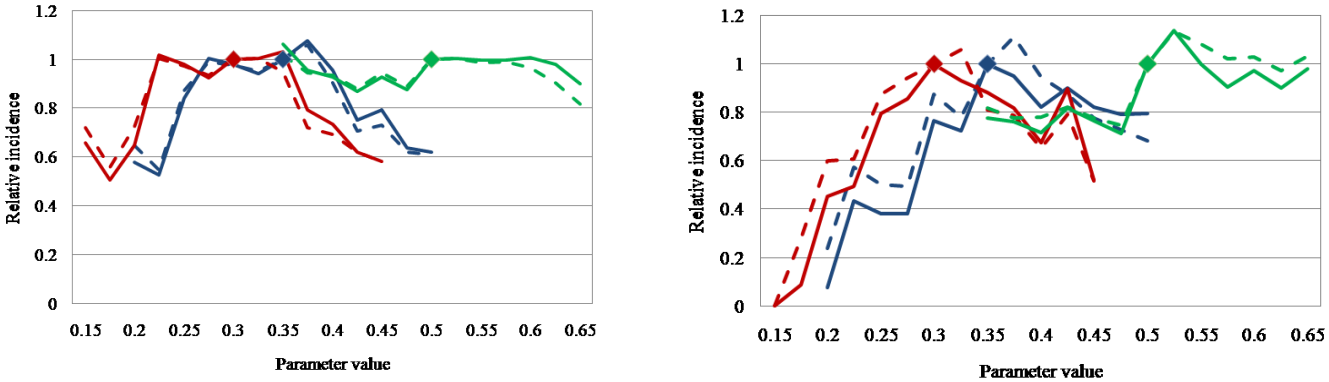
Comparison of the number of apparent cases among two age group categories: school children and older without (a) and with (b) the "unnatural" infection route assumption. Blue and red show school children and 50- years age group categories, respectively.

Figure 9



The transition of incidences for the situation where inapparent cases have no infectiousness without (light blue) and with (orange) the "unnatural" infection route assumption. Four persons each who were infected with a different serotype were introduced into a fully negative population at the beginning.

Figure 10



Relative incidences of apparent (solid line) and inapparent (broken line) dengue cases for various values of parameters compared with those for the adopted values in the present study (diamond mark) without (a) and with (b) the "unnatural" infection route assumption. Blue, red, and green show the situations for variations in the transmission probabilities from vector to human (β), from human to vector (β_V), and the reduction weight of the transmission probability in inapparent cases (y), respectively.

that 3.9% of patients were primary infections and the other 96.1% were re-infection cases [14,15]. These reports suggested that dengue infections in primary infections produced slight symptoms or were asymptomatic, while that in re-infection generated more acute symptoms [3,33]. It was considered that ADE could influence the increased risks of progress to a symptomatic state and increased transmission probability for re-infection. In the model, ADE was assumed to have an influence at any time of re-infection, while Bartley *et al*. [12] and Wearing *et al*. [13] assumed that ADE worked briefly after recovery. In Thailand, the temperature is suitable for *A. aegypti* breeding throughout the year. Because the population of *A. aegypti* was recognized to have seasonal fluctuations [9,10], the model adopted the estimated emergence rates by season according to rainfall, to reflect the transmission capacity of vectors.

In areas such as Thailand where DF is endemic, most cases are infected with DF in childhood, so a significant proportion of children have been infected and obtained immunity to all serotypes [4]. The present model introduced the classification of an age category structure, so that it was possible to examine the incidence of DF by age. The simulation showed that 3.9% of patients were primary infections and the other 96.1% were re-infection cases [14,15]. These reports suggested that dengue infections in primary infections produced slight symptoms or were asymptomatic, while that in re-infection generated more acute symptoms [3,33]. It was considered that ADE could influence the increased risks of progress to a symptomatic state and increased transmission probability for re-infection. In the model, ADE was assumed to have an influence at any time of re-infection, while Bartley *et al*. [12] and Wearing *et al*. [13] assumed that ADE worked briefly after recovery. In Thailand, the temperature is suitable for *A. aegypti* breeding throughout the year. Because the population of *A. aegypti* was recognized to have seasonal fluctuations [9,10], the model adopted the estimated emergence rates by season according to rainfall, to reflect the transmission capacity of vectors.In areas such as Thailand where DF is endemic, most cases are infected with DF in childhood, so a significant proportion of children have been infected and obtained immunity to all serotypes [4]. The present model introduced the classification of an age category structure, so that it was possible to examine the incidence of DF by age. The simulation showed that the number of infected persons decreased in the older categories, and that the incidence in the fifth age category (50 years and over) was extremely small compared with the children's age category (7-12 years) (Figure 8). The effect of an "unnatural" infection route assumption on the dengue epidemic was investigated, which was adopted in the model by Nagao and Koelle [17]. The simulation showed that when the "unnatural" infection route assumption was added, a clear change in dominant serotype occurred on an irregular basis along with sharp and irregular variations in outbreaks, while the dominant serotype changed in a nearly regular rotation without the "unnatural" infection route assumption. Thailand has maintained a dengue epidemic in recent years and a big outbreak has occurred irregularly every few years. It is difficult to predict when severe outbreaks will occur, but they were supposed to be caused by meteorological changes [34] or by the introduction of infected persons from outside the area [35]. The simulation result supported the "unnatural" infection route as having an influence on epidemics of dengue.

It is clear that there are many inapparent cases in DF [14,15], but the role of inapparent cases in dengue transmission is uncertain. A transmission model for DENV, including the inapparently infected class, was constructed to investigate how the inapparent infection affects the prevalence. There was little information about the infectiousness of inapparent cases, although inapparent cases could account for about half of dengue infections [14,15]. When it was assumed that inapparent cases had no infectiousness, a major outbreak occurred once, and afterwards the epidemic diminished immediately (Figure 9), which was not in accord with the actual situation in Thailand. The simulation results under an "unnatural" infection route assumption also agreed with the actual situation in Thailand.

Because its construction was based on the dengue epidemic in Thailand, this dengue transmission model is suited for simulating the transition of dengue epidemic in the circumstances that DF/DHF prevails in all seasons and that all four serotypes of DENV are spread. It can be helpful for analyzing various hypotheses on the transmission process. Further careful research is necessary before the planning of preventive measures against DF, including vector control, because inadequate vector control may strengthen the seriousness of future dengue epidemics.

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Conflict of Interest:

No conflict of interest is declared

Appendix

The model is governed by the following differential equations.

The a runs over the age categories 1-5; the symbol ϕ^a stands for the transfer rate f^a from Nh^a to Nh^{a+1} for a=1, 2, 3, 4 but formally $\phi^0=\phi^5=0$, $\delta_{1,a}$ is 1 for a=1 or 0 for otherwise.

Humans

Primary infection with i –serotype

$$dSh^a_{(0,0,0,0)}/dt = \delta_{1,a}\mu_H Nh+\phi^{a-1}Sh^{a-1}_{(0,0,0,0)}-(\phi^a+\lambda_{H(i)}+\mu_H)Sh^a_{(0,0,0,0)} \quad (A1)$$

$$dEh^a_{(i,0,0,0)}/dt = \phi^{a-1}Eh^{a-1}_{(i,0,0,0)}+\phi^{a-1}\lambda_{H(i)}Sh^{a-1}_{(0,0,0,0)}+(1-\phi^a)\lambda_{H(i)}Sh^a_{(0,0,0,0)} -(\phi^a+\sigma_H+\mu_H)Eh^a_{(i,0,0,0)} \quad (A2)$$

$$dIh^a_{(i,0,0,0)}/dt = \phi^{a-1}Ih^{a-1}_{(i,0,0,0)}+\phi^{a-1}(1-x_1)\sigma_H Eh^{a-1}_{(i,0,0,0)}+(1-\phi^a)(1-x_1)\sigma_H Eh^a_{(i,0,0,0)} -(\phi^a+\gamma_H+\mu_H)Ih^a_{(i,0,0,0)} \quad (A3)$$

$$dIh'^a_{(i,0,0,0)}/dt = \phi^{a-1}Ih'^{a-1}_{(i,0,0,0)}+\phi^{a-1}x_1\sigma_H Eh^{a-1}_{(i,0,0,0)}+(1-\phi^a)x_1\sigma_H Eh^a_{(i,0,0,0)} -(\phi^a+\gamma_H+\mu_H)Ih'^a_{(i,0,0,0)} \quad (A4)$$

$$dCh^a_{(i,0,0,0)}/dt = \phi^{a-1}Ch^{a-1}_{(i,0,0,0)}+\phi^{a-1}\gamma_H(Ih^{a-1}_{(i,0,0,0)}+Ih'^{a-1}_{(i,0,0,0)}) +(1-\phi^a)\gamma_H(Ih^a_{(i,0,0,0)}+Ih'^a_{(i,0,0,0)})-(\phi^a+\delta_H+\mu_H)Ch^a_{(i,0,0,0)} \quad (A5)$$

$$\lambda_{H(i)} = \beta_{H(i)}Iv_{(i)}b/Nh \quad (A6)$$

Re-infection with k–serotype, without an "unnatural" infection route assumption

As an example of the third k–serotype infection after the first i–serotype and the second j–serotype infections, where the serotypes i, j, k are different from each other.

$$dSh^a_{(i,j,0,0)}/dt = \phi^{a-1}Sh^{a-1}_{(i,j,0,0)}+\phi^{a-1}\delta_H Ch^{a-1}_{(i,j,0,0)}+(1-\phi^a)\delta_H Ch^a_{(i,j,0,0)} -(\phi^a+\lambda_{H(k)}+\mu_H)Sh^a_{(i,j,0,0)} \quad (A7)$$

$$dEh^a_{(i,j,k,0)}/dt = \phi^{a-1}Eh^{a-1}_{(i,j,k,0)}+\phi^{a-1}\lambda_{H(k)}Sh^{a-1}_{(i,j,0,0)}+(1-\phi^a)\lambda_{H(k)}Sh^a_{(i,j,0,0)} -(\phi^a+\sigma_H+\mu_H)Eh^a_{(i,j,k,0)} \quad (A8)$$

$$dIh^a_{(i,j,k,0)}/dt = \phi^{a-1}Ih^{a-1}_{(i,j,k,0)}+\phi^{a-1}(1-x_3)\sigma_H Eh^{a-1}_{(i,j,k,0)}+(1-\phi^a)(1-x_3)\sigma_H Eh^a_{(i,j,k,0)} -(\phi^a+\gamma_H+\mu_H)Ih^a_{(i,j,k,0)} \quad (A9)$$

$$dIh'^a_{(i,j,k,0)}/dt = \phi^{a-1}Ih'^{a-1}_{(i,j,k,0)}+\phi^{a-1}x_3\sigma_H Eh^{a-1}_{(i,j,k,0)}+(1-\phi^a)x_3\sigma_H Eh^a_{(i,j,k,0)} -(\phi^a+\gamma_H+\mu_H)Ih'^a_{(i,j,k,0)} \quad (A10)$$

$$dCh^a_{(i,j,k,0)}/dt = \phi^{a-1}Ch^{a-1}_{(i,j,k,0)}+\phi^{a-1}\gamma_H(Ih^{a-1}_{(i,j,k,0)}+Ih'^{a-1}_{(i,j,k,0)}) +(1-\phi^a)\gamma_H(Ih^a_{(i,j,k,0)}+Ih'^a_{(i,j,k,0)})-(\phi^a+\delta_H+\mu_H)Ch^a_{(i,j,k,0)} \quad (A11)$$

$$\lambda_{H(k)} = \chi_{(k)}\beta_{H(k)}Iv_{(k)}b/Nh \quad (A12)$$

Re-infection with k-serotype, with an "unnatural" infection route assumption

Applying the "unnatural" infection route assumption, equations (A5), (A7) and (A10) are replaced as (A5'), (A7') and (A10') and the new equation (A13) was added.

$$dCh^a_{(i,0,0,0)}/dt = \phi^{a-1}Ch^{a-1}_{(i,0,0,0)}+\phi^{a-1}\gamma_H(Ih^{a-1}_{(i,0,0,0)}+Ih'^{a-1}_{(i,0,0,0)}) +(1-\phi^a)\gamma_H(Ih^a_{(i,0,0,0)}+Ih'^a_{(i,0,0,0)})-(\phi^a+\lambda_{H(k)}+\delta_H+\mu_H)Ch^a_{(i,0,0,0)} \quad (A5')$$

$$dSh^a_{(i,j,0,0)}/dt = \phi^{a-1}Sh^{a-1}_{(i,j,0,0)}+\phi^{a-1}(1-\Sigma'_{k3}\,\lambda_{H(k)}Ch^{a-1}_{(i,j,0,0)})+(1-\phi^a)(1-\Sigma'_k\,\lambda_{H(k)}Ch^a_{(i,j,0,0)}) -(\phi^a+\lambda_{H(k)}+\mu_H)Sh^a_{(i,j,0,0)} \quad (A7')$$

$$dEh'^a_{(i,j,k,0)}/dt = \phi^{a-1}Eh'^{a-1}_{(i,j,k,0)}+\phi^{a-1}\lambda_{H(k)}Ch^{a-1}_{(i,j,0,0)}+(1-\phi^a)\lambda_{H(k)}Ch^a_{(i,j,0,0)} -(\phi^a+\sigma_H+\mu_H)Eh'^a_{(i,j,k,0)} \quad (A13)$$

$$dIh'^a_{(i,j,k,0)}/dt = \phi^{a-1}Ih'^{a-1}_{(i,j,k,0)}+\phi^{a-1}\sigma_H(x_3Eh^{a-1}_{(i,j,k,0)}+Eh^{a-1}_{(i,j,k,0)}) +(1-\phi^a)\sigma_H(x_3Eh^a_{(i,j,k,0)}+Eh^a_{(i,j,k,0)})-(\phi^a+\gamma_H+\mu_H)Ih'^a_{(i,j,k,0)} \quad (A10')$$

Here, Σ'_k means the summation of all k-serotypes except i, j.

Vector infection with i -serotype

$$dSv/dt = \mu_V Nv-(\lambda_{V(i)}+\mu_V)Sv \quad (A14)$$

$$dEv_{(i)}/dt = \lambda_{V(i)}Sv-(\sigma_V+\mu_V)Ev_{(i)} \quad (A15)$$

$$dIv_{(i)}/dt = \sigma_V Ev_{(i)}-\mu_V Iv_{(i)} \quad (A16)$$

$$\lambda_{V(i)} = \beta_{V(i)}\,(total(Ih^a_{(i)})+y\ total(Ih'^a_{(i)}))b/Nh \quad (A17)$$

Here, $total(Ih^a_{(i)})$ or $total(Ih'^a_{(i)})$ runs over all age-categories (a = 1, …, 5) and all possible combinations of j, k, l in (i,0,0,0), (j,i,0,0), (j,k,i,0), (j,k,l,i) for the epidemiological classes Ih or Ih'.