Proceeding Series of the Brazilian Society of Computational and Applied Mathematics, v. 10, n. 1, 2023.

Trabalho apresentado no XLII CNMAC, Universidade Federal de Mato Grosso do Sul - Bonito - MS, 2023

Proceeding Series of the Brazilian Society of Computational and Applied Mathematics

A co-infection model for multi-strain dynamics of dengue virus with temporary cross-immunity

Shyam S. Das[1], Claudia M. Dias[2]
PPGMMC, UFRRJ, Seropédica, RJ
Dayse H. Pastore[3]
CEFET-RJ, Rio de Janeiro, RJ

Abstract Dengue virus (DENV) belongs to the *Flaviviridae* family and is an RNA virus that is primarily spread by *Aedes aegypti* mosquitoes. In this paper, we propose a new multi-strain dengue transmission model that accounts for temporary cross-immunity and co-infection. We developed an in-house MATLAB code and performed simulations for different epidemic scenarios. We conduct numerical simulations of the model for two different epidemic scenarios, one without temporary cross-immunity and one with temporary cross-immunity, to gain deeper insights into the complex dynamics of dengue transmission with multiple strains. Our results reveal that strain 3 has a higher basic reproduction number than the other two strains, indicating that it is more transmissible. We also observe a unique pattern in the infection curve for the human population due to the effects of cross-immunity and co-infection with strains 1 and 2, which initially decreases but then increases again, reaching a peak approximately 180 days after the initial infections. Our findings suggest that the proposed model can be useful in predicting the transmission dynamics of dengue with multiple strains.

Keywords Dengue Virus, Cross-immunity. Co-infection, Multi-strain Dynamics

1 Introduction

Dengue virus (DENV) is transmitted primarily by*Aedes aegypti* and *Aedes albopictus* mosquitoes [1]. While *Aedes aegypti* mosquitoes are the primary vector for DENV transmission in urban areas, *Aedes albopictus* mosquitoes are commonly found in rural and suburban environments. DENV comprises five distinct strains, and individuals in endemic regions may be infected by any of these strains throughout their lives [2, 1]. Once recovered from a specific strain, a person gains lifelong immunity to it, while only acquiring temporary immunity to the other strains. This temporary cross-protection lasts between three and nine months and is marked by elevated antibody levels that defend against further infections [2, 1]. However, if someone is re-infected with a different DENV strain after recovery, they may face a heightened risk of severe clinical outcomes compared to those encountering their first infection, due to a phenomenon called antibody-dependent enhancement (ADE) [2, 1]. The spread of dengue has become a major public health concern, and efforts to control the disease have focused on mosquito control, vaccine development, and improved clinical management [2, 1].

Many authors propose various mathematical models to study multi-strain dynamics of dengue transmission models [3, 4, 5, 2]. Esteva and Vargas worked on two strain dynamics of the dengue

[1] das.shyamsumanta@gmail.com
[2] mazza@ufrrj.br
[3] daysepastore@gmail.com

 © 2023 SBMAC

model and discusses the asymptotic stability of the model [3]. The authors studied the coexistence of multiple serotypes [4]. Feng et al. studied a 2-strain DENV model with temporary cross-immunity. The authors investigated the co-existence of competing strains [1]. The authors [6] studied the complex dynamics in multiserotype disease models by inducing ADE effect. Aguiar et al. developed a multi-strain DENV model with temporary cross-immunity. The authors investigated the presence of bifurcations and chaotic behavior in the wide range of model parameters [7]. Mishra and Gakkar [2] studied a two-strain DENV model and investigated the primary and secondary dengue infections. Zheng and Nie [8] developed a 2-strain DENV model with vector control and awareness of susceptible human strategies. Xue et al. [9] studied the multi-strain dynamics with temporary cross-immunity. The authors [9] investigated the local and global stability analysis of disease-free equilibrium, boundary equilibrium, and interior equilibrium points.

None of these researchers [7, 10, 3, 4, 5, 2] have modeled co-infections (the presence of multiple dengue strains at a time) in their models. Some authors [11] reported the presence of co-infections with multiple dengue serotypes for the first time in Hyderabad during the year 2014. This means that individuals in Hyderabad, India, were infected with more than one dengue serotype at the same time, which is known as a co-infection. Senaratne et al. [12] investigated the clinical presentation and laboratory findings of dengue virus (DENV) infected patients with co-infections from three provinces in Sri Lanka. It is important to note that the findings of this study are based on limited sample size and a specific geographic location, so the results may not be generalizable to other populations or settings. Further research with larger sample sizes and more diverse populations is needed to validate and expand upon these findings.

In this work, we aimed to better understand the multi-strain dynamics of dengue virus transmission and the role of cross-immunity in shaping the epidemiology of the disease. By developing a co-infection model that incorporates temporary cross-immunity and performing simulations for various scenarios, we were able to accurately capture the transmission dynamics of the disease.

2 Mathematical Model

The set of differential equations from Equations (1-7) represents the co-infection model for multi-strain dynamics of 3 DENV strains with temporary cross-immunity. We assume the homogeneity in the host and vector populations. The model assumes that individuals who are infected with one strain of DENV will have temporary immunity to the other strains, but this immunity wanes over time.

$$\frac{dS}{dt} = \tau_h - S\sum_{i=1}^{3}\beta_{1i}I_{vi} - \mu S \tag{1}$$

$$\frac{dI_i}{dt} = S\beta_{1i}I_{vi} - (\mu + \alpha_i + d_i)I_i \tag{2}$$

$$\frac{dR_i}{dt} = \alpha_i I_i - (\mu + \sum_{j=1,j\neq i}^{3}\beta_{2j}I_{vj})R_i \tag{3}$$

$$\frac{dI_{2i}}{dt} = \sum_{j=1,j\neq i}^{3}\beta_{2j}I_{vj}R_i - (\mu + \alpha_i + d_i)I_{2i} \tag{4}$$

$$\frac{dR}{dt} = \sum_{j=1}^{3}\alpha_j I_{2j} - \mu R \tag{5}$$

 © 2023 SBMAC

$$\frac{dS_v}{dt} = \tau_v - S_v(\sum_{i=1}^{3} \beta_{vi}(I_i + \sum_{j=1, j\neq i}^{3} I_{2j})) - \mu_v S_v \tag{6}$$

$$\frac{dI_{vi}}{dt} = S_v(\beta_{vi}(I_i + \sum_{j=1, j\neq i}^{3} I_{2j})) - \mu_v I_{vi} \tag{7}$$

Here, $i, j = 1, 2, 3$. In this model, the state variables are S: Susceptible human Population,I_{1i}: Infected human population bitten by infected mosquitoes with strain i, $i = 1, 2, 3$, R_i: Recovered human population from strain i, I_{2i}: Infected human population, recovered from strain i but bitten by infected mosquito j, $j \neq i$, S_v: Susceptible mosquitoes population, I_{vi}: Infected mosquitoes population by strain i. $N(t) = S(t) + \sum_{i=1}^{3} I_i(t) + \sum_{i=1}^{3} R_i(t) + \sum_{i=1}^{3} I_{2i}(t) + R(t)$ and $N_v(t) = S_v(t) + \sum_{i=1}^{3} I_{vi}(t)$. $N(t)$ is the total human population and $N_v(t)$ is the total mosquito population.

The model parameters are β_{1i}: Transmission rate between susceptible human and infected mosquitoes with strain i, β_{2i}: Transmission rate between recovered human from strain i and infected mosquitoes with strain j, $j \neq i$, β_{vi}: Transmission rate between susceptible mosquitoes and infected human population with strain i, τ_h: Total birth rate of the human population, μ: Mortality rate of the human population, α_i: Recovery rate of human population from strain i, d_i: Induced mortality rate in humans due dengue infection, τ_v: Total birth rate of mosquito population, μ_v: Mortality rate of the mosquito population.

In the proposed model, the susceptible human population S is exposed to the infected mosquitoes I_{vj} $(j = 1, 2, 3)$. The infected mosquitoes I_{vj} are infected with the strain j. Then the susceptible human enters the infected compartment I_i. After staying $(\frac{1}{\alpha_i})$ days, the infected person with strain i recovers and enters into the compartment R_i. The recovered person from strain i, then enters into the period of temporary cross-immunity. During this time the person gets temporary immunity from strain j, where $(j \neq i)$. The time for temporary cross-immunity is 3 to 9 months. After 9 months, the recovered person from strain i will again be susceptible to other strains (j and k, $i \neq j, k$). In the model, we assume the effect of co-infection after the temporary cross-immunity time period. The co-infection arises due to the presence of multiple strains in the host. After infection from infected mosquitoes $I_{vj} + I_{vk}$ (i is not equal to j and k), it will enter into the secondary infected compartment I_{2i} $(i = 1, 2, 3)$. Then, after staying for $(1/\alpha_i)$ days, it will recover from the secondary infection and enter into the recovered compartment R. In the mosquito dynamics, the susceptible mosquito (S_v) will be exposed to the infected human from primary and secondary infection $(I_i + I_{2j} + I_{2k})$ with transmission rate β_{vj}. In the model, we include the human total birth rate (τ_h) and death rate (μ) and mosquito birth rate (τ_v), and death rates (μ_v).

3 Results and Discussion

In this section, we presented the numerical results of our proposed three-strain dengue transmission model for two different epidemic scenarios. In Case 1, we assumed no impact of temporary cross-immunity among the DENV strains, while in Case 2, we accounted for this effect. Through numerical simulations, we aimed to gain a deeper understanding of how the three strains interact and influence disease transmission. The model parameters were sourced from the study by [9] and our analysis of the two scenarios provided valuable insights into the complex dynamics of dengue transmission.

For the case 1, the model parameters values for the human population are $\tau_h = 0.2$, $\beta_{11} = 1.303 \times 10^{-5}$, $\beta_{12} = 3 * \beta_{11}$, $\beta_{13} = 1.324 \times 10^{-5}$, $\beta_{21} = 0$, $\beta_{22} = 0$, $\beta_{23} = 0$, $\alpha_i = 0.4$, $\mu = \frac{1}{70\times365}$, $i = 1, 2, 3$. The model parameters values for mosquito population are: $\tau_v = 1000$, $\mu_v = \frac{1}{14}$, $\beta_{v1} = 2.9\times10^{-5}$, $\beta_{v2} = 3\times10^{-5}$, $\beta_{v3} = 3.2\times10^{-5}$. The initial conditions for the case 1 are $S(0) = \frac{\tau_h}{\mu} - 2$,

 © 2023 SBMAC

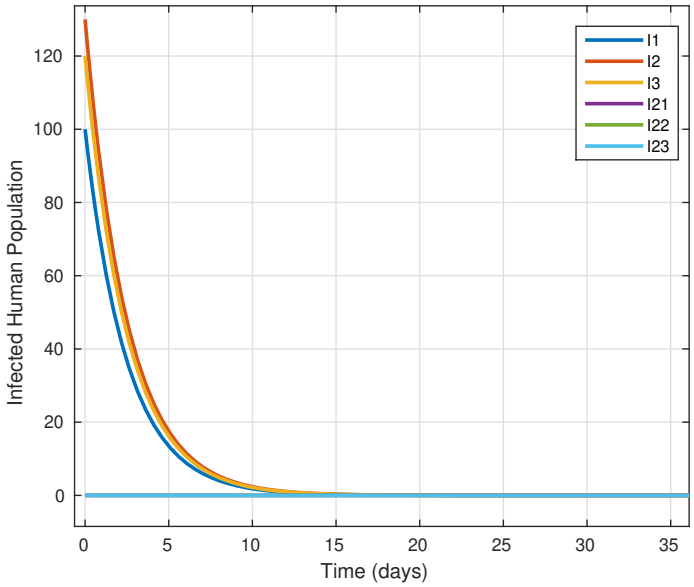
$I_1(0) = 100$, $I_2(0) = 130$, $I_3(0) = 120$, $R_1(0) = 40$, $R_2(0) = 38$, $R_3(0) = 30$, $I_{21}(0) = 0$, $I_{22}(0) = 0$, $I_{23}(0) = 0$, $R(0) = 0$, $S_v(0) = \frac{\tau_h}{\mu} - 200$, $I_{v1}(0) = 100$, $I_{v2}(0) = 140$, $I_{v3}(0) = 150$. The infected human population with all three strains eventually died out, reaching the disease-free equilibrium (DFE) as shown in Figure 2(a). It means for case 1, the basic reproduction number $R_i, i = 1, 2, 3$ for the three DENV strains is less than one. It is also interesting to note that the infection curves for mosquito population also approach DFE, see Figure 2(b).

For the second case, we have considered the cross-immunity and co-infections in the model. The model parameters values for human population are : $\tau_h = 0.2$, $\beta_{11} = 2 \times 10^{-3}$, $\beta_{12} = 3 \times 10^{-3}$, $\beta_{13} = 5 \times 10^{-3}$, $\beta_{21} = 0.6 \times \beta_{11}$, $\beta_{22} = 0.8 \times \beta_{12}$, $\beta_{23} = 0.7 \times \beta_{13}$, $\alpha_i = 0.4$, $\mu = \frac{1}{70 \times 365}$, $i = 1, 2, 3$. The model parameters values for mosquito population are: $\tau_v = 1000$, $\mu_v = \frac{1}{14}$, $\beta_{v1} = 2.9 \times 10^{-3}$, $\beta_{v2} = 3 \times 10^{-3}$, $\beta_{v3} = 3.2 \times 10^{-3}$. The initial conditions for the case 1 are $S(0) = \frac{\tau_h}{\mu} - 2000$, $I_1(0) = 100$, $I_2(0) = 130$, $I_3(0) = 120$, $R_1(0) = 40$, $R_2(0) = 38$, $R_3(0) = 30$, $I_{21}(0) = 100$, $I_{22}(0) = 120$, $I_{23}(0) = 140$, $R(0) = 80$, $S_v(0) = \frac{\tau_h}{\mu} - 200$, $I_{v1}(0) = 100$, $I_{v2}(0) = 140$, $I_{v3}(0) = 150$. It has been observed that the effect of temporary cross-immunity of 3 DENV strains on the population, see Figure 2. It is interesting to note that the infected human population due to infected mosquitoes with strain 1 and 2 are dying out. The infection curve for I_{13} due to DENV strain 3, initially it is declining then suddenly it is rising again and stabilizes in the population. It means the dengue infection due to strain 3 persists for a longer period of time. The rise in primary infection in the human population is attributed due to the higher transmission rate of strain 3, see Figure 2(a). It is worth noting that the infection curve for the human population I_{23} exhibits a unique pattern due to the effects of cross-immunity and co-infection with strains 1 and 2. Specifically, this curve initially decreases, but then increases again, reaching a peak approximately 180 days after the initial infections. This peak coincides with the average time period for temporary cross-immunity, as reported in a study by [9]. It shows the presence of secondary infections in the human population. Figure 2(b) illustrates the temporal evolution of the infected mosquito population due to the three strains, taking into account the effects of temporary cross-immunity. Numerical simulations indicate that the infection caused by DENV strain 3 initially increases and then stabilizes in the mosquito population, while the infections caused by the other strains decline over time. Both Figure 2(a) and 2(b) indicate that the basic reproduction number for strains 1 and 2 is less than one, while for strain 3 it is greater than one, suggesting that strain 3 is more transmissible than other two strains.

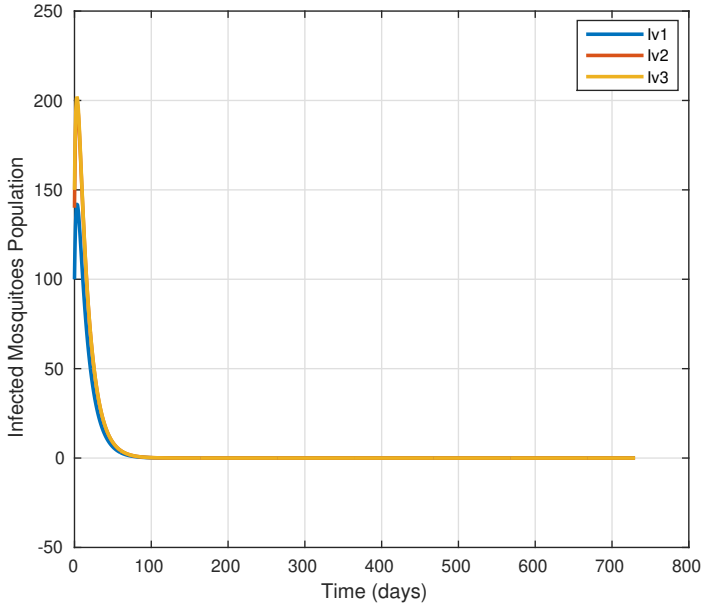
4 Conclusion

In this paper, we proposed a new multi-strain dengue transmission model that accounts for temporary cross-immunity and co-infection. Our simulations revealed insights into the complex dynamics of dengue transmission with multiple strains. Specifically, we found that strain 3 has a basic reproduction number greater than one, indicating that it is more transmissible than the other two strains. In addition, the infection curve for the human population due to strain 3 persists for a longer period of time, while the infections caused by the other strains decline over time. Furthermore, we observed an interesting effect of cross-immunity and co-infection due to strains 1 and 2, which resulted in a unique pattern in the infection curve for the human population. Overall, our findings suggest that the proposed model can be useful in predicting the transmission dynamics of dengue with multiple strains and in designing effective control strategies. In future work, we plan to conduct a stability analysis and explore invasion scenarios within the context of serotypes competition. We aim to investigate the principles of competitive exclusion, which pertain to the ability of certain serotypes to outcompete others. By studying these dynamics, we hope to gain a deeper understanding of how different serotypes interact and potentially invade a given system.

 © 2023 SBMAC



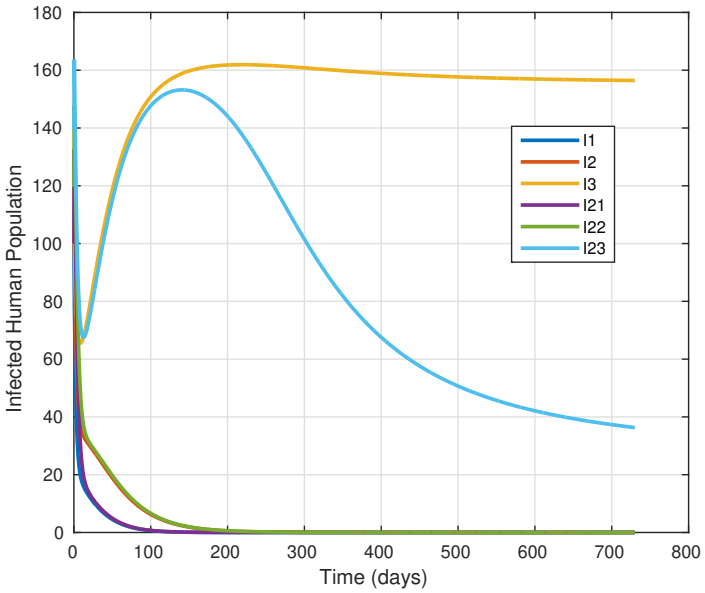
(a) Infected human population by strains 1,2 and 3



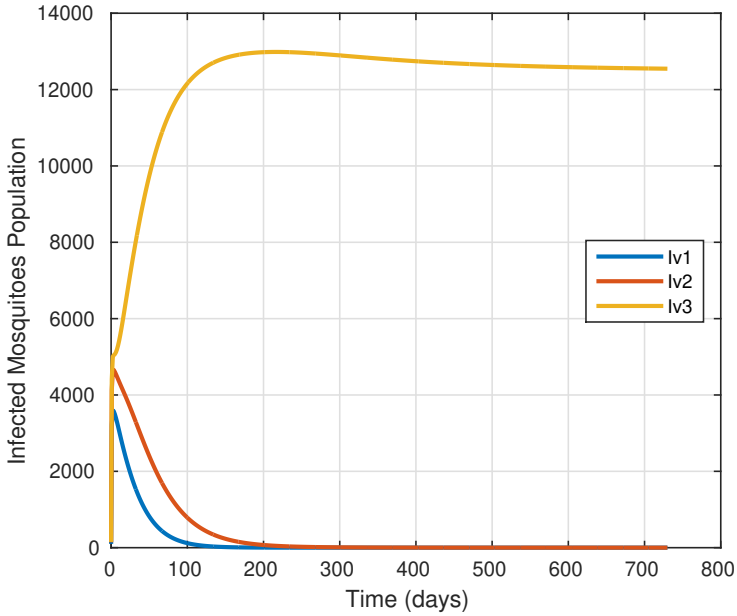
(b) Infected mosquito population by strains 1, 2 and 3

Figure 1: Infected human and mosquitoes population by strains 1, 2 and 3

 © 2023 SBMAC



(a) Infected human population by strains 1,2 and 3



(b) Infected mosquito population by strains 1, 2 and 3

Figure 2: Infected human and mosquitoes population by strains 1, 2 and 3

DOI: 10.5540/03.2023.010.01.0007 © 2023 SBMAC

5 Acknowledgment

I would like to express my sincere gratitude to the Brazilian research funding agency CAPES for their generous support of my research work. I am grateful to my research supervisors, Prof. Claudia Dias and Prof. Dayse Pastore for their support.

References

[1] Z. Feng and J. X. Velasco-Hernández, "Competitive exclusion in a vector-host model for the dengue fever," *Journal of mathematical biology*, vol. 35, pp. 523–544, 1997.

[2] A. Mishra and S. Gakkhar, "The effects of awareness and vector control on two strains dengue dynamics," *Applied Mathematics and Computation*, vol. 246, pp. 159–167, 2014.

[3] L. Esteva and C. Vargas, "Analysis of a dengue disease transmission model," *Mathematical biosciences*, vol. 150, no. 2, pp. 131–151, 1998.

[4] L. Esteva and C. Vargas, "Coexistence of different serotypes of dengue virus," *Journal of mathematical biology*, vol. 46, no. 1, pp. 31–47, 2003.

[5] M. Aguiar and N. Stollenwerk, "Mathematical models of dengue fever epidemiology: multi-strain dynamics, immunological aspects associated to disease severity and vaccines," *Communication in Biomathematical Sciences*, vol. 1, no. 1, pp. 1–12, 2017.

[6] L. Billings, I. B. Schwartz, L. B. Shaw, M. McCrary, D. S. Burke, and D. A. T. Cummings, "Instabilities in multiserotype disease models with antibody-dependent enhancement," *Journal of theoretical biology*, vol. 246, no. 1, pp. 18–27, 2007.

[7] M. Aguiar, S. Ballesteros, B. W. Kooi, and N. Stollenwerk, "The role of seasonality and import in a minimalistic multi-strain dengue model capturing differences between primary and secondary infections: complex dynamics and its implications for data analysis," *Journal of theoretical biology*, vol. 289, pp. 181–196, 2011.

[8] T. Zheng and L. Nie, "Modelling the transmission dynamics of two-strain dengue in the presence awareness and vector control," *Journal of theoretical biology*, vol. 443, pp. 82–91, 2018.

[9] L. Xue, H. Zhang, W. Sun, and C. Scoglio, "Transmission dynamics of multi-strain dengue virus with cross-immunity," *Applied Mathematics and Computation*, vol. 392, p. 125742, 2021.

[10] N. Anggriani, H. Tasman, M. Z. Ndii, A. K. Supriatna, E. Soewono, and E. Siregar, "The effect of reinfection with the same serotype on dengue transmission dynamics," *Applied Mathematics and Computation*, vol. 349, pp. 62–80, 2019.

[11] K. Vaddadi, C. Gandikota, P. K. Jain, V. S. V. Prasad, and M. Venkataramana, "Co-circulation and co-infections of all dengue virus serotypes in hyderabad, india 2014," *Epidemiology & Infection*, vol. 145, no. 12, pp. 2563–2574, 2017.

[12] U. T. N. Senaratne, K. Murugananthan, P. D. N. N. Sirisena, J. M. Carr, and F. Noordeen, "Dengue virus co-infections with multiple serotypes do not result in a different clinical outcome compared to mono-infections," *Epidemiology & Infection*, vol. 148, 2020.

 © 2023 SBMAC