

## Modeling and $R_0$ estimation of the 2010 Dengue Hemorrhagic Fever Outbreak in Hermosillo Sonora.

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We model and estimate the basic reproductive number of Dengue and Dengue Hemorrhagic Fever outbreak of the 2010 from Hermosillo Sonora. Our results suggest that serotype DENV-2 of the Dengue virus and the cross infection risk enhancement hypothesis, could explain the incidence of Dengue Hemorrhagic Fever cases reported by Secretaria de Salud del Estado de Sonora.

**Keywords:** Differential Equations; Dengue Hemorrhagic Fever; Boot strap;

### 1. Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

**OBJECTIVES** Our objective is to explain the dengue hemorrhagic outbreak that occurred in the city of Hermosillo, located in the state of Sonora in 2010.

**SEVERITY** Dengue Classic Fever (DCF) Dengue Hemorrhagic Fever (DHF) description.

**ADE HYPOTHESIS** Dengue Virus Serotype 1 (DENV-1), Dengue Virus Serotype 2 (DENV-2) reinfection as cause of hemorrhagic.

### BACKGROUND

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## 2. Material and methods

It was reported that in 2010 there was present only DENV-1 circulating Hermosillo (Tesis de Pablo. La referencia que menciona ya no se encuentra disponible por internet.)

## 3. Material and methods

Provide sufficient detail to allow the work to be reproduced, with details of supplier and catalogue number when appropriate. Methods already published should be indicated by a reference: only relevant modifications should be described.

### 3.1 Data

#### DATA DESCRIPTION (PABLO)

SOCIOECONOMIC DESCRIPTION: HOMOGENEITY OF REGARDING INITIAL GROW GEOGRAPHIC AREA■  
(ANA-LUCIA)

#### Model

Our work aims to explain the DHF cases reported in the Hermosillo's 2010 outbreak. Particularly, our aim is to provide evidence based on a mathematical model and statistical parameter estimation that a second strain (DENV-2) was also present in the city in 2010, and thus being responsible for the presence of DHF.

Thus, our formulation only considers the time of the epidemic and supposes that at this period, the DENV-2 serotype invades for the first time the city. We understand the DHF cases as a consequence of reinfection with the DENV-2 serotype. That is, a fraction of individuals with immunity to serotype DENV-1—acquired by past outbreaks—increments their susceptibility to the DENV-2, and consequently develops hemorrhagic with a certain probability.

#### Important Hypothesis (Daniel-Saúl)

**PERMANENT IMMUNITY** Accordingly to WHO ((1997 (accessed May, 2018)), infection of Dengue caused by a serotype DEN-i induces long-life immunity to reinfection with this strain. Then, we assume in our formulation that a susceptible individual previously infected with Dengue of serotype DEN-i only could acquire Dengue of a different serotype. We also suppose that a susceptible individual who never get infected before, could obtain Dengue by any of serotypes DENV-1, or DENV-2, but only for a single time and during the outbreak period.

**ADE HYPOTHESIS** The processes and factors that produce DHF are still unclear. There is evidence that reinfection with a different serotype enhances the probability of developing plasma vascular permeability—the Antibody Dependent infection Enhancement (ADE) hypothesis ((see, e.g. Halstead, 1992, p. 295)). But there also exist studies that report first infection DHF cases Streatfield et al. ((1993)). We consider in our formulation the ADE hypothesis, that is, only a fraction of the second reinfection with serotype DENV-2 develops vascular leaking.

**DENV-2 REPORT CIRCULATION IN HERMOSILLO** According to Vázquez-Pichardo et al. ((2011)) and Reyes-Castro et al. ((2017)), in year 2010 only DENV-1 was present in the state of Sonora. Based on this information it is not clear that reinfection with a second strain in 2010 is the main cause of DHF. However, contrary to these studies, one of the main hypothesis in this work is that DENV-2 was present in Sonora in 2010. Our hypothesis is based on previous experiences, just as mentioned in Gómez Dantés et al. ((2014)). In this work, where the authors analyze the dengue situation in Mexico for the period 2000 to 2011, argue that the increase of DHF in 2001 in Yucatan was linked to the introduction of the DENV-2 strain. Therefore, part of our hypothesis is that in 2010 there was an introduction of the DENV-2 into the Sonora state.

**ASYMPTOMATIC AND REPORTED CASES** We assume that the 95% (pendiente) of the DCF are asymptomatic, whereas for DHF all the cases are reported. Therefore, the class  $Y_{-1}^{[h]}$  accounts for all the DHF cases, whereas a fraction  $p = 0.05$  of the sum  $I_1 + I_2 + Y_{-1}^{[c]}$  represent the confirmed cases of DCF.

Incluir citas de los porcentajes de asintomáticos, <http://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue> says that about 75% is asymptomatic

chastel2012.pdf

**HOMOGENEITY ABOUT THE EARLY OUTBREAK STAGE** Define the infection forces as

$$\begin{aligned} A_{I_1} &= \frac{\beta_M b}{N_H} I_1, & A_{I_2} &= \frac{\beta_M b}{N_H} I_2, \\ A_{Y_{-1}^{[h]}} &= \frac{\beta_M b}{N_H} Y_{-1}^{[h]}, & A_{Y_{-1}^{[c]}} &= \frac{\beta_M b}{N_H} Y_{-1}^{[c]}, \\ B_{M_1} &= \frac{\beta_H b}{N_H} M_1, & B_{M_2} &= \frac{\beta_H b}{N_H} M_2. \end{aligned} \quad (3.1)$$

**VECTOR TRANSMISSION DYNAMICS** Define

$$A_{\bullet} := A_{I_1} + A_{I_2} + A_{Y_{-1}^{[h]}} + A_{Y_{-1}^{[c]}}$$

as the total human infection force, that is, the sum of all human contributions to the vector infection. Then we describe the mosquito disease dynamics by

$$\begin{aligned} \frac{dM_S}{dt} &= \Lambda_M - A_{\bullet} M_S - \mu_M M_S \\ \frac{dM_1}{dt} &= A_{I_1} M_S - \mu_M M_1 \\ \frac{dM_2}{dt} &= \left( A_{I_2} + A_{Y_{-1}^{[h]}} + A_{Y_{-1}^{[c]}} \right) M_S - \mu_M M_2 \end{aligned} \quad (3.2)$$

Here  $M_S$ , is the vector susceptible class and  $M_1$ ,  $M_2$  respectively denotes the vector Infected classes with DENV-1 and DENV-2.

**HOST DISEASE DYNAMICS** Susceptible individuals ( $S$ ) become infected for the first time with DENV-1 or DENV-2 after a successful mosquito bite and move to classes  $I_1$  and  $I_2$ , respectively. From here,

they remain in the infected class for  $1/\alpha_c$  time units, after which, move to a recovered class  $R_S$ . As we are interested in a one year dynamics, for the rest of the epidemic they become immune to any serotype. A second class of susceptible individuals  $S_{-1}$ , consist on those who acquired DENV-1 in previous years and in the current year are susceptible only to DENV-2. Such individuals become infected with DENV-2 when exposed to infected mosquitoes with that serotype. In OhAinle et al. ((2011)) and Sangkawibha et al. ((1984)) it was observed that a more severe version of dengue occurs (might occur?) when an individual acquires dengue for a second time, and this happens to be DENV-2. Based on this assumption, an individual from  $S_{-1}$  moves to  $Y_{-1}^{[c]}$  or  $Y_{-1}^{[h]}$ , if the infection leads to DF or DHF, respectively. Finally, these infected individuals move to the recovered class  $R_{S_{-1}}$  at rates  $\alpha_c$  and  $\alpha_h$ , respectively. For our model,  $\mu_H$  is the human death rate;  $b$  is the number of bites per week per mosquito and  $\beta_H$  is the effectiveness of the bite. From the current hypothesis our model is given by

$$\begin{aligned}
 \frac{dS}{dt} &= \mu_H N_S - (B_{M_1} + B_{M_2})S - \mu_H S \\
 \frac{dI_1}{dt} &= B_{M_1}S - (\alpha_c + \mu_H)I_1 \\
 \frac{dI_2}{dt} &= B_{M_2}S - (\alpha_c + \mu_H)I_2 \\
 \frac{dR_S}{dt} &= \alpha_c I_2 - \mu_H R_S \\
 \frac{dS_{-1}}{dt} &= \mu_H N_{S_{-1}} - \sigma B_{M_2}S_{-1} - \mu_H S_{-1} \\
 \frac{dY_{-1}^{[c]}}{dt} &= (1 - \theta)\sigma B_{M_2}S_{-1} - (\alpha_c + \mu_H)Y_{-1}^{[c]} \\
 \frac{dY_{-1}^{[h]}}{dt} &= \theta\sigma B_{M_2}S_{-1} - (\alpha_h + \mu_H)Y_{-1}^{[h]} \\
 \frac{dR_{S_{-1}}}{dt} &= \alpha_c Y_{-1}^{[c]} + \alpha_h Y_{-1}^{[h]} - \mu_H R_{S_{-1}}
 \end{aligned} \tag{3.3}$$

Here, we take  $N_H = N_S + N_{S_{-1}}$  as the total number of individuals. For our formulation  $N_H, N_S$  and  $N_{S_{-1}}$  remain constant.  $N_S$  is the total number of individuals that are involved in the first infection dynamics ( $N_S = S + I_1 + I_2 + R_S$ ). On the other hand  $N_{S_{-1}}$  is the total number of individuals involved in the reinfection dynamics ( $N_{S_{-1}} = S_{-1} + Y_{-1}^{[c]} + Y_{-1}^{[h]} + R_{S_{-1}}$ ). Also, the recovered individuals in both classes can be considered as a single recovered class  $R = R_S + R_{S_{-1}}$  as our dynamics are taken only for one year. Then, our equations become

$$\begin{aligned}
\frac{dS}{dt} &= \mu_H N_S - (B_{M_1} + B_{M_2})S - \mu_H S \\
\frac{dI_1}{dt} &= B_{M_1}S - (\alpha_c + \mu_H)I_1 \\
\frac{dI_2}{dt} &= B_{M_2}S - (\alpha_c + \mu_H)I_2 \\
\frac{dS_{-1}}{dt} &= \mu_H N_{S_{-1}} - \sigma B_{M_2}S_{-1} - \mu_H S_{-1} \\
\frac{dY_{-1}^{[c]}}{dt} &= (1 - \theta)\sigma B_{M_2}S_{-1} - (\alpha_c + \mu_H)Y_{-1}^{[c]} \\
\frac{dY_{-1}^{[h]}}{dt} &= \theta\sigma B_{M_2}S_{-1} - (\alpha_h + \mu_H)Y_{-1}^{[h]} \\
\frac{dR}{dt} &= \alpha_c (I_1 + I_2 + Y_{-1}^{[c]}) + \alpha_h Y_{-1}^{[h]} - \mu_H R
\end{aligned} \tag{3.4}$$

Fix  $A_{-1} = N_{-1}$ .

Include information about the 2 strains

Symbol	Meaning
$M_S$	Number of susceptible mosquitoes.
$M_1, M_2$	Number of infected mosquitoes with virus serotype DENV-1 or DENV-2.
$S$	Susceptible host population which, never has acquired dengue.
$S_{-1}$	Susceptible host population which is immune to serotype 1.
$I_1, I_2$	First time infected host population by serotype 1 and 2, respectively.
$Y_{-1}^{[h]}, Y_{-1}^{[c]}$	Second time infected host population with serotype 2, with DHF and DCF, respectively.

Table 1: Meaning of variables. Here we omit the explicit dependence of time.

BASIC REPRODUCTIVE NUMBER The disease free equilibrium results

$$FDE = \left( \frac{\Lambda_M}{\mu_M}, 0, 0, N_H - N_{S_{-1}}, 0, N_{S_{-1}}, 0, 0, 0 \right).$$

Using the next generation operator method reported as in Feng and Velasco-Hernández ((1997)), we

get a relation for the initial grow phase parameter

obtain the basic reproductive number

$$\begin{aligned}
 \pi_R &:= \frac{\beta_H \beta_M b^2 \Lambda_M}{\mu_M^2 N_H^2} \\
 R_{01} &:= \pi_R \left( \frac{N_H - N_{S-1}}{\alpha_c + \mu_H} + \frac{(1 - \theta) \sigma N_{S-1}}{\alpha_c + \mu_H} \right) \\
 R_{02} &:= \pi_R \frac{\sigma \theta N_{S-1}}{\alpha_h + \mu_H}, \\
 \mathcal{R}_0 &:= \sqrt{R_{01} + R_{02}}.
 \end{aligned} \tag{3.5}$$

$$\begin{aligned}
 \psi &:= \frac{\beta_M b N_M}{\mu_M N_H} \\
 R_{0c} &:= \sqrt{\psi \left( \frac{\beta_H b N_S}{(\alpha_c + \mu_H) N_H} + \frac{\beta_H b (1 - \theta) \sigma N_{S-1}}{(\alpha_c + \mu_H) N_H} \right)} \\
 R_{0h} &:= \sqrt{\left( \frac{\beta_M b N_M}{\mu_M N_H} \right) \left( \frac{\sigma \theta N_{S-1}}{(\alpha_h + \mu_H) N_H} \right)} \\
 \mathcal{R}_0 &:= \sqrt{R_{0c}^2 + R_{0h}^2}.
 \end{aligned} \tag{3.6}$$

In this equation,  $R_{0c}$  and  $R_{0h}$ , are the basic reproductive numbers for classical and hemorrhagic dengue cases, respectively. From here,  $R_0$  provides a measure of how DF and DHF infected people influence the presence of new dengue cases (Either DF or DHF).  $R_{0h}$  measures the new hemorrhagic cases that arise from one hemorrhagic infected individual in a population of  $N_{S-1}$  susceptible to strain 2 individuals, meanwhile  $R_{0c}$  provides a measure of how many new individuals will obtain DC fever (DF?) from an individual that has or has not have acquired dengue previously (from an individual that has either DF or DHF).

Observe that this  $R_0$  differs in some way to the traditional  $R_0$  where two different serotypes are involved (Feng and Velasco-Hernández ((1997)) include citations of  $R_0$  for two serotypes). This follows from the idea that we are interested in classic and hemorrhagic cases rather than the predominance of a serotype.

Discuss above parameters units. Weeks or days

### 3.2 $R_0$ estimation (Montoya)

$$\frac{dZ}{dt} = p \left( I_1 + I_2 + Y_{-1}^{[c]} \right). \tag{3.7}$$

## 4. Results

Results should be clear and concise.

MODELING RESULTS (SAÚL-DANIEL)

DATA ANALYSIS (SAÚL-MONTOYA)

Symbol	Meaning	Reference	Range	units
$M_S(0)$	Initial number of susceptible and infected			
$M_1(0)$	mosquitoes.			
$M_2(0)$				
$N_H$	Total Susceptible population	INEGI (see section 5)	283 493	
$b$	Biting rate	Yasuno M ((1990))	[10.36 , 33.39]	meals/week
$\Lambda_S$	Human birth rate		$\mu_H \cdot (N_H - N_{S-1})$	week <sup>-1</sup>
$\Lambda_{S-1}$	Human birth rate		$\mu_H \cdot N_{S-1}$	week <sup>-1</sup>
$\Lambda_M$	Vector birth rate		$\mu_M \cdot N_M$	week <sup>-1</sup>
$\mu_M$	vector mortality rate	YANG et al. ((2009))	[0.252, 0.763]	week <sup>-1</sup>
$\mu_H$	Human mortality	—	0.000 273 973	week <sup>-1</sup>
$\beta_H$	Human infection probability by vectors	Feng and Velasco-Hernández ((1997))	(0, 0.05]	—
$\beta_M$	Vector infection probability by humans	Feng and Velasco-Hernández ((1997))	(0, 0.05]	—
$\alpha_c$	Mean recover rate from Classic Dengue	Pinho et al. ((2010))	[0.581, 1.75]	week <sup>-1</sup>
$\alpha_h$	Mean recover rate from Hemorrhagic Dengue	Pinho et al. ((2010))	[0.581, 1.75]	week <sup>-1</sup>
$\sigma$	Susceptibility to serotype DENV-2.	Feng and Velasco-Hernández ((1997))	(0, 5)	
$p$	Ratio of asymptomatic cases	Balmaseda et al. ((2006)), Chastel ((2011, 2012))	$[\frac{1}{60}, \frac{1}{30}]$	—
$\theta$	Probability of acquire DHF as second infection			

Table 2: Parameter description

 $R_0$  AND PARAMETER INFERENCE (MONTROYA)**5. Discussion**

## DATA DESCRIPTION (PABLO)

## SOCIOECONOMIC DESCRIPTION: HOMOGENEITY ACCORDING TO POPULATION DENSITY INDEX

## Model

Our work aims to explain the DHF cases reported in the Hermosillo's 2010 outbreak. Particularly, our aim is to provide evidence based on a mathematical model and statistical parameter estimation that a second strain (DENV-2) was also present in the city in 2010, and thus being responsible for the presence of DHF.

Thus, our formulation only considers the time of the epidemic and supposes that at this period, the DENV-2 serotype invades for the first time the city. We understand the DHF cases as a conse-

Parameters (time in weeks) for figs. 5 and 6		
$\Lambda_M = 30702.6139006,$	$\Lambda_S = 10.2385934233,$	$\Lambda_{S_{-1}} = 1.13762149148,$
$\alpha_c = 0.686615937276,$	$\alpha_h = 1.41310092256,$	$b = 12.7122333418,$
$\beta_H = 0.0478488977733,$	$\beta_H = 0.0478488977733,$	$\beta_M = 0.0361065995648,$
$\mu_H = 0.000273,$	$\mu_M = 0.307170720093,$	
$\sigma = 1.806480946,$		
$\theta = 0.1887501857,$		
$p = 0.126295209216,$	$h = 0.000189285714286,$	
$S(0) = 35598.0,$	$I_1(0) = 1.0,$	$I_2(0) = 1.0,$
$M_S(0) = 120000,$	$M_1(0) = 10,$	$M_2(0) = 10,$
$S_{-1}(0) = 4400.0,$	$Y_{-1}^{[c]}(0) = 0.0,$	
$Y_{-1}^{[h]}(0) = 0.0,$	$z(0) = 0.252590418433,$	$Rec(0) = 0.0,$

Table 3: Parameters of numerical example

quence of reinfection with the DENV-2 serotype. That is, a fraction of individuals with immunity to serotype DENV-1—acquired by past outbreaks—increments their susceptibility to the DENV-2, and consequently develops hemorrhagic with a certain probability.

### Important Hypothesis (Daniel-Saúl)

**PERMANENT IMMUNITY** Accordingly to WHO ((1997 (accessed May, 2018))), infection of Dengue caused by a serotype DEN-i induces long-life immunity to reinfection with this strain. Then, we assume in our formulation that a susceptible individual previously infected with Dengue of serotype DEN-i only could acquire Dengue of a different serotype. We also suppose that a susceptible individual who never get infected before, could obtain Dengue by any of serotypes DENV-1, or DENV-2, but only for a single time and during the outbreak period.

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**VECTOR TRANSMISSION DYNAMICS** Define

$$A_{\bullet} := A_{I_1} + A_{I_2} + A_{Y_{-1}^{[h]}} + A_{Y_{-1}^{[c]}}$$

as the total human infection force, that is, the sum of all human contributions to the vector infection. Then we describe the mosquito disease dynamics by

$$\begin{aligned} \frac{dM_S}{dt} &= \Lambda_M - A_{\bullet} M_S - \mu_M M_S \\ \frac{dM_1}{dt} &= A_{I_1} M_S - \mu_M M_1 \\ \frac{dM_2}{dt} &= \left( A_{I_2} + A_{Y_{-1}^{[h]}} + A_{Y_{-1}^{[c]}} \right) M_S - \mu_M M_2 \end{aligned} \quad (5.2)$$

Here  $M_S$ , is the vector susceptible class and  $M_1$ ,  $M_2$  respectively denotes the vector Infected classes with DENV-1 and DENV-2.

**HOST DISEASE DYNAMICS** Susceptible individuals ( $S$ ) become infected for the first time with DENV-1 or DENV-2 after a successful mosquito bite and move to classes  $I_1$  and  $I_2$ , respectively. From here, they remain in the infected class for  $1/\alpha_c$  time units, after which, move to a recovered class  $R_S$ . As we are interested in a one year dynamics, for the rest of the epidemic they become immune to any serotype. A second class of susceptible individuals  $S_{-1}$ , consist on those who acquired DENV-1 in previous years and in the current year are susceptible only to DENV-2. Such individuals become infected with DENV-2 when exposed to infected mosquitoes with that serotype. In OhAinle et al. ((2011)) and Sangkawibha et al. ((1984)) it was observed that a more severe version of dengue occurs (might occur?) when an individual acquires dengue for a second time, and this happens to be DENV-2. Based on this assumption,

an individual from  $S_{-1}$  moves to  $Y_{-1}^{[c]}$  or  $Y_{-1}^{[h]}$ , if the infection leads to DF or DHF, respectively. Finally, these infected individuals move to the recovered class  $R_{S_{-1}}$  at rates  $\alpha_c$  and  $\alpha_h$ , respectively. For our model,  $\mu_H$  is the human death rate;  $b$  is the number of bites per week per mosquito and  $\beta_H$  is the effectiveness of the bite. From the current hypothesis our model is given by

$$\begin{aligned}
 \frac{dS}{dt} &= \mu_H N_S - (B_{M_1} + B_{M_2})S - \mu_H S \\
 \frac{dI_1}{dt} &= B_{M_1}S - (\alpha_c + \mu_H)I_1 \\
 \frac{dI_2}{dt} &= B_{M_2}S - (\alpha_c + \mu_H)I_2 \\
 \frac{dR_S}{dt} &= \alpha_c I_2 - \mu_H R_S \\
 \frac{dS_{-1}}{dt} &= \mu_H N_{S_{-1}} - \sigma B_{M_2}S_{-1} - \mu_H S_{-1} \\
 \frac{dY_{-1}^{[c]}}{dt} &= (1 - \theta)\sigma B_{M_2}S_{-1} - (\alpha_c + \mu_H)Y_{-1}^{[c]} \\
 \frac{dY_{-1}^{[h]}}{dt} &= \theta\sigma B_{M_2}S_{-1} - (\alpha_h + \mu_H)Y_{-1}^{[h]} \\
 \frac{dR_{S_{-1}}}{dt} &= \alpha_c Y_{-1}^{[c]} + \alpha_h Y_{-1}^{[h]} - \mu_H R
 \end{aligned} \tag{5.3}$$

Here, we take  $N_H = N_S + N_{S_{-1}}$  as the total number of individuals. For our formulation  $N_H, N_S$  and  $N_{S_{-1}}$  remain constant.  $N_S$  is the total number of individuals that are involved in the first infection dynamics ( $N_S = S + I_1 + I_2 + R_S$ ). On the other hand  $N_{S_{-1}}$  is the total number of individuals involved in the reinfection dynamics ( $N_{S_{-1}} = S_{-1} + Y_{-1}^{[c]} + Y_{-1}^{[h]} + R_{S_{-1}}$ ). Also, the recovered individuals in both classes can be considered as a single recovered class  $R = R_S + R_{S_{-1}}$  as our dynamics are taken only for one year. Then, our equations become

$$\begin{aligned}
 \frac{dS}{dt} &= \mu_H N_S - (B_{M_1} + B_{M_2})S - \mu_H S \\
 \frac{dI_1}{dt} &= B_{M_1}S - (\alpha_c + \mu_H)I_1 \\
 \frac{dI_2}{dt} &= B_{M_2}S - (\alpha_c + \mu_H)I_2 \\
 \frac{dS_{-1}}{dt} &= \mu_H N_{S_{-1}} - \sigma B_{M_2}S_{-1} - \mu_H S_{-1} \\
 \frac{dY_{-1}^{[c]}}{dt} &= (1 - \theta)\sigma B_{M_2}S_{-1} - (\alpha_c + \mu_H)Y_{-1}^{[c]} \\
 \frac{dY_{-1}^{[h]}}{dt} &= \theta\sigma B_{M_2}S_{-1} - (\alpha_h + \mu_H)Y_{-1}^{[h]} \\
 \frac{dR}{dt} &= \alpha_c (I_1 + I_2 + Y_{-1}^{[c]}) + \alpha_h Y_{-1}^{[h]} - \mu_H R
 \end{aligned} \tag{5.4}$$

Symbol	Meaning
$M_S$	Number of susceptible mosquitoes.
$M_1, M_2$	Number of infected mosquitoes with virus serotype DENV-1 or DENV-2.
$S$	Susceptible host population which, never has acquired dengue.
$S_{-1}$	Susceptible host population which is immune to serotype 1.
$I_1, I_2$	First time infected host population by serotype 1 and 2, respectively.
$Y_{-1}^{[h]}, Y_{-1}^{[c]}$	Second time infected host population with serotype 2, with DHF and DCF, respectively.

Table 4: Meaning of variables. Here we omit the explicit dependence of time.

BASIC REPRODUCTIVE NUMBER The disease free equilibrium results

$$FDE = \left( \frac{\Lambda_M}{\mu_M}, 0, 0, N_H - N_{S_{-1}}, 0, N_{S_{-1}}, 0, 0, 0 \right).$$

Using the next generation operator method reported as in Feng and Velasco-Hernández ((1997)), we obtain the basic reproductive number

get a relation for the initial grow phase parameter

$$\begin{aligned}
 \pi_R &:= \frac{\beta_H \beta_M b^2 \Lambda_M}{\mu_M^2 N_H^2} \\
 R_{01} &:= \pi_R \left( \frac{N_H - N_{S_{-1}}}{\alpha_c + \mu_H} + \frac{(1 - \theta) \sigma N_{S_{-1}}}{\alpha_c + \mu_H} \right) \\
 R_{02} &:= \pi_R \frac{\sigma \theta N_{S_{-1}}}{\alpha_h + \mu_H}, \\
 \mathcal{R}_0 &:= \sqrt{R_{01} + R_{02}}. \\
 \psi &:= \frac{\beta_M b N_M}{\mu_M N_H} \\
 R_{0c} &:= \sqrt{\psi \left( \frac{\beta_H b N_S}{(\alpha_c + \mu_H) N_H} + \frac{\beta_H b (1 - \theta) \sigma N_{S_{-1}}}{(\alpha_c + \mu_H) N_H} \right)} \\
 R_{0h} &:= \sqrt{\left( \frac{\beta_M b N_M}{\mu_M N_H} \right) \left( \frac{\sigma \theta N_{S_{-1}}}{(\alpha_h + \mu_H) N_H} \right)} \\
 \mathcal{R}_0 &:= \sqrt{R_{0c}^2 + R_{0h}^2}.
 \end{aligned} \tag{5.5}$$

In this equation,  $R_{0c}$  and  $R_{0h}$ , are the basic reproductive numbers for classical and hemorrhagic dengue cases, respectively. From here,  $R_0$  provides a measure of how DF and DHF infected people

influence the presence of new dengue cases (Either DF or DHF).  $R_{0h}$  measures the new hemorrhagic cases that arise from one hemorrhagic infected individual in a population of  $N_{S-1}$  susceptible to strain 2 individuals, meanwhile  $R_{0c}$  provides a measure of how many new individuals will obtain DC fever (DF?) from an individual that has or has not have acquired dengue previously (from an individual that has either DF or DHF).

Observe that this  $R_0$  differs in some way to the traditional  $R_0$  where two different serotypes are involved (Feng and Velasco-Hernández ((1997)) include citations of  $R_0$  for two serotypes). This follows from the idea that we are interested in classic and hemorrhagic cases rather than the predominance of a serotype.

Symbol	Meaning	Reference	Range	units
$M_S(0)$ $M_1(0)$ , $M_2(0)$	Initial number of susceptible and infected mosquitoes.			
$N_H$	Total Susceptible population	INEGI (see section 5)	283 493	
$b$	Biting rate	Yasuno M ((1990))	[10.36 , 33.39]	meals/week
$\Lambda_S$	Human birth rate		$\mu_H \cdot (N_H - N_{S-1})$	week <sup>-1</sup>
$\Lambda_{S-1}$	Human birth rate		$\mu_H \cdot N_{S-1}$	week <sup>-1</sup>
$\Lambda_M$	Vector birth rate		$\mu_M \cdot N_M$	week <sup>-1</sup>
$\mu_M$	vector mortality rate	YANG et al. ((2009))	[0.252, 0.763]	week <sup>-1</sup>
$\mu_H$	Human mortality	—	0.000 273 973	week <sup>-1</sup>
$\beta_H$	Human infection probability by vectors	Feng and Velasco-Hernández ((1997))	(0, 0.05]	—
$\beta_M$	Vector infection probability by humans	Feng and Velasco-Hernández ((1997))	(0, 0.05]	—
$\alpha_c$	Mean recover rate from Classic Dengue	Pinho et al. ((2010))	[0.581, 1.75]	week <sup>-1</sup>
$\alpha_h$	Mean recover rate from Hemorrhagic Dengue	Pinho et al. ((2010))	[0.581, 1.75]	week <sup>-1</sup>
$\sigma$	Susceptibility to serotype DENV-2.	Feng and Velasco-Hernández ((1997))	(0, 5)	
$p$	Ratio of asymptomatic cases	Balmaseda et al. ((2006)), Chastel ((2011, 2012))	$[\frac{1}{60}, \frac{1}{30}]$	—
$\theta$	Probability of acquire DHF as second infection			

Table 5: Parameter description

Discuss above parameters units. Weeks or days

### 5.1 $R_0$ estimation (Montoya)

We suppose that the number of cases of classic and hemorrhagic dengue are observed at time points  $t_1, \dots, t_n$ . Here we assume that these processes, denoted by  $X_t$  and  $Y_t$  respectively, follow a Poisson

Parameters (time in weeks) for figs. 5 and 6		
$\Lambda_M = 30\,702.613\,9006$ ,	$\Lambda_S = 10.238\,593\,423\,3$ ,	$\Lambda_{S-1} = 1.137\,621\,491\,48$ ,
$\alpha_c = 0.686\,615\,937\,276$ ,	$\alpha_h = 1.413\,100\,922\,56$ ,	$b = 12.712\,233\,341\,8$ ,
$\beta_H = 0.047\,848\,897\,773\,3$ ,	$\beta_H = 0.047\,848\,897\,773\,3$ ,	$\beta_M = 0.036\,106\,599\,564\,8$ ,
$\mu_H = 0.000\,273$ ,	$\mu_M = 0.307\,170\,720\,093$ ,	
$\sigma = 1.806\,480\,946$ ,		
$\theta = 0.188\,750\,185\,7$ ,		
$p = 0.126\,295\,209\,216$ ,	$h = 0.000\,189\,285\,714\,286$ ,	
$S(0) = 35\,598.0$ ,	$I_1(0) = 1.0$ ,	$I_2(0) = 1.0$ ,
$M_S(0) = 120\,000$ ,	$M_1(0) = 10$ ,	$M_2(0) = 10$ ,
$S_{-1}(0) = 4400.0$ ,	$Y_{-1}^{[c]}(0) = 0.0$ ,	
$Y_{-1}^{[h]}(0) = 0.0$ ,	$z(0) = 0.252\,590\,418\,433$ ,	$Rec(0) = 0.0$ ,

Table 6: Parameters of numerical example

distribution with mean  $\lambda_h(t) = Y_{-1}^{[h]}$  and  $\lambda_c(t) = Z$ , where

$$\frac{dZ}{dt} = p \left( I_1 + I_2 + Y_{-1}^{[c]} \right). \quad (5.7)$$

In our case the vector of parameters of the ordinary differential equations model is  $\phi = (\phi_1, \phi_2)$ , where  $\phi_1 = (\beta_H, \beta_M)$  is regarded as unknown and  $\phi_2 = (\alpha_c, \alpha_h, b, \mu_H, \mu_M, \sigma, \theta, p)$  is known in advance. We write  $\lambda_h(t)$  and  $\lambda_c(t)$  as  $\lambda_h(t; \phi_1)$  and  $\lambda_c(t; \phi_1)$  to emphasize this fact.

We use the likelihood approach to estimate the vector parameter  $\psi_1$  based on the observed samples  $\vec{x} = (x_{t_1}, \dots, x_{t_n})$  and  $\vec{y} = (y_{t_1}, \dots, y_{t_n})$ . The resulting likelihood function is thus

$$L(\phi_1) = \prod_{i=1}^n \left\{ \frac{1}{x_{t_i}!} [\lambda_h(t_i; \phi_1)]^{x_{t_i}} \exp[-\lambda_h(t_i; \phi_1)] \frac{1}{y_{t_i}!} [\lambda_c(t_i; \phi_1)]^{y_{t_i}} \exp[-\lambda_c(t_i; \phi_1)] \right\}. \quad (5.8)$$

The maximum likelihood estimate (MLE) of  $\phi_1$  is that value of  $\phi_1$  that maximizes  $L(\phi_1)$  in (5.8). We denote the MLE of  $\phi_1$  as  $\hat{\phi}_1$ .

We now consider profile-likelihood inference based on (1) for estimating the parameters of interest ( $R_{01}$ ,  $R_{02}$ , and  $\mathcal{R}_0$ ). Here we assume without loss of generality that  $\phi_1 = (\beta_H, \beta_M)$  can be rewritten as  $\phi_1 = (\gamma, \eta)$ , where  $\gamma$  is a scalar parameter of interest and  $\eta$  is a scalar nuisance parameter. For example, we may only be interested in  $R_{01}$ . In this case, we can rewrite the parameter  $\beta_M$  as a function of the parameters  $R_{01}$  and  $\beta_H$ ,

$$\beta_M = C \frac{R_{01}}{\beta_H},$$

where

$$C = \left[ \left( \frac{N_H - N_{S-1}}{\alpha_c + \mu_H} + \frac{(1 - \theta)\sigma N_{S-1}}{\alpha_c + \mu_H} \right) \left( \frac{b^2 \Lambda_M}{\mu_M^2 N_H^2} \right) \right]^{-1}$$

Thus, we reparametrize the model in terms of  $\phi_1 = (\gamma, \eta) = (R_{01}, \beta_H)$ , where  $\gamma = R_{01}$  is the parameter of interest and  $\eta = \beta_H$  is the nuisance parameter.

The profile likelihood and its corresponding relative likelihood function of  $\gamma$ , standardized to be one at the maximum of the likelihood function, are

$$L_{\max}(\gamma) = \max_{\eta} L(\phi_1 = (\gamma, \eta)),$$

$$R_{\max}(\gamma) = \frac{L_{\max}(\gamma)}{\max_{\phi_1} L(\phi_1)},$$

where  $L(\cdot)$  is the likelihood function given in (5.8). In particular, the relative profile likelihood varies between 0 and 1 and ranks all possible  $\gamma$  values based only on the observed samples  $\vec{x} = (x_{t_1}, \dots, x_{t_n})$  and  $\vec{y} = (y_{t_1}, \dots, y_{t_n})$ . Thus, a graph of  $R_{\max}(\gamma)$  allows to distinguish plausible and implausible values for  $\gamma$ .

A level  $\omega$  profile likelihood region (commonly an interval) for  $\gamma$  is given by

$$\{\gamma : R_{\max}(\gamma) \geq \omega\},$$

where  $0 \leq \omega \leq 1$ . We can assign a confidence level to the profile likelihood region of  $\gamma$  considering the asymptotical behavior of the likelihood ratio statistic  $D = -2 \ln R_{\max}(\gamma_0)$ . This is an asymptotic pivotal quantity having a Chi-squared distribution with one degree of freedom. Thus, approximate confidence levels of 99%, 95% and 90% can be ascribed to profile likelihood regions at  $\omega = 0.036, 0.146$ , and  $0.25$ , respectively.

## 6. Results

Results should be clear and concise.

MODELING RESULTS (SAÚL-DANIEL)

DATA ANALYSIS (SAÚL-MONTOYA)

$R_0$  AND PARAMETER INFERENCE (MONTOYA)

## 7. Discussion

This should explore the significance of the results of the work, not repeat them. A combined results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

In our results we obtained  $R_{0c} > 1$  and  $R_{0h} < 1$ . This means that for this outbreak, the presence of DHF cases, cannot trigger on its own new DHF cases and in general,  $R_{0h} < 1$  would imply an exponential decay on the number of infected individuals. However, the small DHF outbreak arises despite the value of  $R_{0h}$  as there is an increase in infected mosquitoes of the serotype 2 due to the presence of the  $S$  individuals, which initially is close to  $N_S$ . Therefore, DHF dynamics is a consequence of the intensity of the outbreak of DF, given by serotype 2.

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IN THE DISCUSSION-CONCLUSIONS IT IS ESSENTIAL TO:

- be clear what YOU did and what other authors have done
- highlight your UNIQUE contribution
- discuss LIMITATIONS of your findings state what the applications and implications of your research are

The Discussion should answer the following questions, and possibly in the following order. You can thus use the answers to structure your Discussion. This gives you a relatively easy template to follow.

1. What are my most important findings?
2. Do these findings support what I set out to demonstrate at the beginning of the paper?
3. How do my findings compare with what others have found? How consistent are they?
4. What is my personal interpretation of my findings?
5. What other possible interpretations are there?
6. What are the limitations of my study? What other factors could have influenced my findings? Have I reported everything that could make my findings invalid?
7. Do any of the interpretations reveal a possible flaw (i.e. defect, error) in my experiment?
8. Do my interpretations contribute some new understanding of the problem that I have investigated? In which case do they suggest a shortcoming in, or an advance on, the work of others?
9. What external validity do my findings have? How could my findings be generalized to other areas?
10. What possible implications or applications do my findings have? What support can I give for such implications?
11. What further research would be needed to explain the issues raised by my findings? Will I do this research myself or do I want to throw it open to the community?

A JBM structure for discussion:

STATEMENT OF PRINCIPAL FINDINGS The central hypotheses of this manuscript were:

- strain DENV-II circulated in the 2010 Hermosillo
- Dengue outbreak antibody-Dependent Enhancement hypothesis could explain the HDF high incidence
- unconfirmed cases represent almost 95 % of the total incidence.

With these hypotheses, we formulated a model that describes the incidence dynamics of HDF cases of the 2010 Hermosillo outbreak. Our parameters estimation does not reject these hypothesis and provide statistical evidence that the concerning reproductive number was 2.47.

**STRENGTHS AND WEAKNESSES OF THE STUDY** Our  $R_0$  estimation is consistent with the outbreak reported in [\*]. We believe this is the first attempt to fit the exponential growth of the incidence according to the severity of Dengue Disease. Further the structure of our  $R_0$  calculation results to be the geometric mean of the expression that are closely related with the parameters transmission according to the Hemorrhagic.

We apply the idea of an index of strain susceptibility as in [1,2,3] to modulate the propensity to acquire Dengue due to a given serotype. Thus, combining the hypothesis of unreported incidence [3,4,5], we achieve proper data fitting.

However, our formulation only considers an outbreak of one season. Thus classical asymptotic analysis has mathematical consistency but lacks biological meaning. In this line, we are preparing a version that achieves both— proper data fitting and consistent asymptotic behavior. We believe that adding a class of immunity according to the particular strain would be an option.

Our contribution describes scenarios wherein past Dengue outbreaks detected a dominant strain. Then decision-makers could project new dengue strain invasion scenarios.

The cause of HDF is still unclear; for example, in [6] reports that the concentration of the virus explains the severity of Dengue. In this direction, Gomez et al. report a model that considers a severity stratification according to the mosquito load virulence.

In short, we believe that early serotype identification in any Dengue outbreak would be essential information to make epidemiological decisions.

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**STRENGTHS AND WEAKNESSES IN RELATION TO OTHER STUDIES, DISCUSSING IMPORTANT DIFFERENCES IN RESULTS**

**MEANING OF THE STUDY: POSSIBLE EXPLANATIONS AND IMPLICATIONS FOR CLINICIANS AND POLICYMAKERS**

**UNANSWERED QUESTIONS AND FUTURE RESEARCH**

**HIGHLIGHTING OUR FINDING**

## 8. Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

In this work we have presented a mathematical model to understand the 2010 dengue outbreak that occurred in Hermosillo, Mexico. The model includes infected classes of classic and hemorrhagic versions of dengue in order to adjust the observed data. To our knowledge, there is no published work. In this work we have presented a mathematical model to understand the 2010 dengue outbreak that occurred in Hermosillo, Mexico. The model includes infected classes of classic and hemorrhagic versions of dengue in order to adjust the observed data. To our knowledge, there is no published work.

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disiase\_flow.pdf

Figure 1: Flow diagram of model (??)



Figure 2: DF and DHF numerical solutions versus Dengue data from 2010 Hermosillo outbreak. Python code and data in <https://github.com/SaulDiazInfante/Two-strains-dengue-model-data-fitting/tree/master/StochasticSearchPySimplifiedModel>

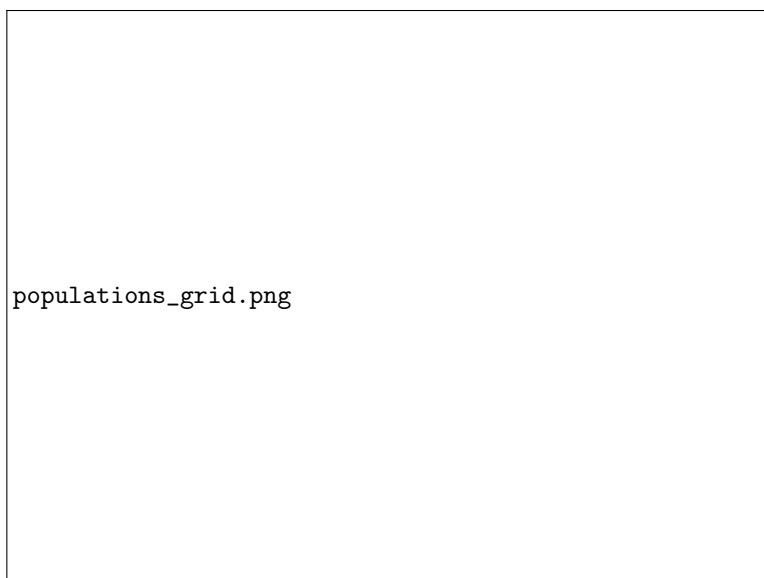


Figure 3: Evolutions of each stage.

disiase\_flow.pdf

Figure 4: Flow diagram of model (??)



Figure 5: DF and DHF numerical solutions versus Dengue data from 2010 Hermosillo outbreak. Python code and data in <https://github.com/SaulDiazInfante/Two-strains-dengue-model-data-fitting/tree/master/StochasticSearchPySimplifiedModel>

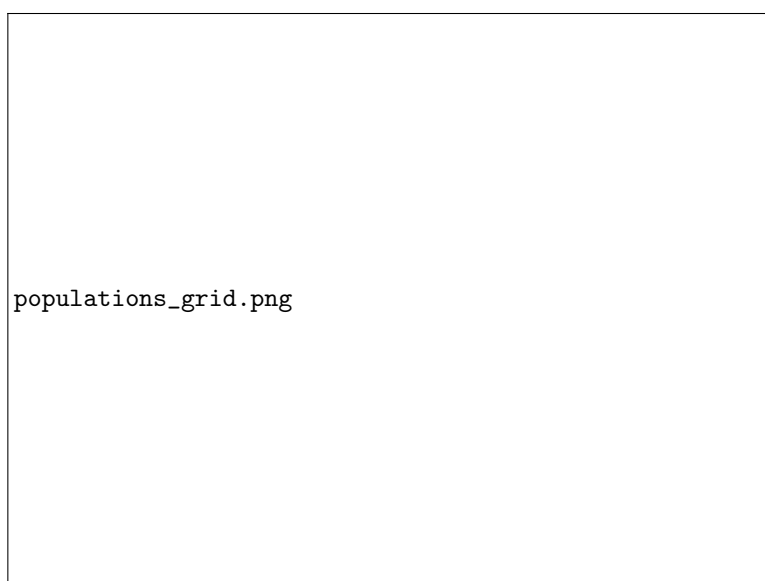


Figure 6: Evolutions of each stage.