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A Mathematical Model for Dengue Fever in a Virgin Environment

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0. Abstract

In this paper, a system of differential equations is used as a virus dynamics model, based off a Dengue epidemics model proposed by Pinho et. Al (2010). A 2009 Cape Verde epidemic, the first in that country's history, is chosen as the outbreak for this study because of its unique characteristics: a virgin environment with no immunities or increased susceptibilities to the various Dengue serotypes, and the existence of a single serotype throughout the epidemic. Due to this novel incidence of Dengue in Cape Verde and to minimal reporting, the data set for the epidemic is sparse. However, this shortcoming is dealt with by using an extended logistic model-fitting technique. Certain key parameters' values in the differential equations model can then be found based on this fitting. Other parameters are taken from previous studies in similar environments. With these, the basic reproductive rate (R_0) can be calculated, giving a numerical measure of this particular epidemic's infectiousness. The validity of this differential equation model is then tested by comparing generated values to the fitted data. This paper represents the first attempt in existing literature to carefully apply existing Dengue models and theory to such a virgin environment.

1. Introduction

(a) Dengue Virus

Dengue is a mosquito-borne viral infection found in tropical and subtropical regions around the world. The disease was named in 1779 and the first recorded epidemics of it occurred simultaneously on three continents within the following decade.[1] Dengue Fever (DF) is characterized by flu-like symptoms that are generally reported as quite unpleasant – but usually not fatal. One colloquial name for the illness, "breakbone fever", comes from the excruciating bone pain that victims sometimes feel. However, in some cases patients can contract a more serious form of the disease, known as Dengue Hemorrhagic Fever (DHF), which is far more dangerous. The World Health Organization estimates that today over 2.5 billion people are at risk for Dengue (over 40% of the world's population). Between 50 and 100 million cases of traditional Dengue occur globally per year, with an estimated additional 500,000 cases of the hemorrhagic variation.[2] Four decades ago, the disease was endemic in only nine countries. Currently it is endemic in more than 100 countries, and is spreading.

A variety of characteristics complicate any attempt to study or model the Dengue virus. Foremost among these is that the virus exists in four serotypes (distinct variations/antigen combinations within the same virus species): DENV-1, DENV-2, DENV-3, and DENV-4. Infection from one serotype grants life-long immunity to that strain, and also appears to temporarily grant the host a degree of cross-protection. However, ultimately the recovered patient will become more susceptible to the other three forms.[3] [4] There is also an elevated risk of contracting Dengue Hemorrhagic Fever from a secondary infection. Furthermore, endemic Dengue tends to appear cyclically, with each outbreak separated by several years. Thus, populations where Dengue is endemic (such as many parts of Asia and Latin America) and several serotypes exist are exceedingly difficult to accurately represent with a single mathematical model.

(b) Aedes aegypti

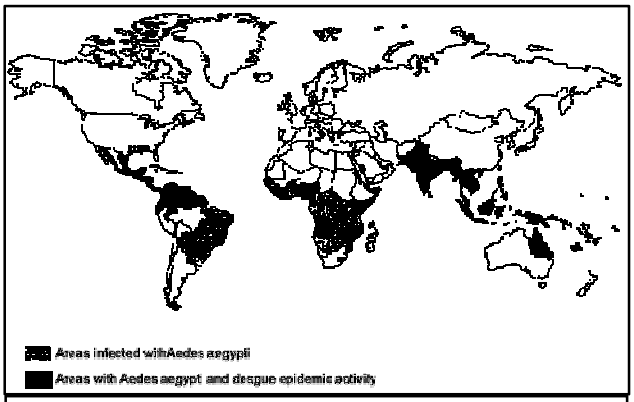

Figure 1 - Global Distribution of Ae. aegypti (WHO)

Aedes aegypti is a type of mosquito that lives predominantly between the 45°N and 40°S latitudes (and is present in 23 states in the US).[5] The species is believed to have originated in Africa, and has been a nuisance to many countries around the world for centuries (Figure 1). It is also the primary vector for both the Dengue Virus and Yellow Fever. These mosquitoes' average lifespan is only eight days, but this increases to between two and four weeks with warm and wet conditions. Three different domestic forms of Aedes aegypti exist, preferring urban, sylvan and farmland environments, respectively. Adult males and females range in size from 4-7 millimeters and they feed primarily on plant nectar. However, after impregnation, females must take a blood meal within 24-36 hours in order to produce eggs. (Blood provides the protein necessary for egg maturation.) After a blood meal, a female mosquito will lay between 100 and 200 eggs, and can repeat this cycle up to four more times in her lifetime. The most important factors in population sizes of Aedes aegypti are temperature, availability of stagnant water and blood sources, and elevation.[6]

Several traits of Aedes aegypti make it particularly dangerous as a Dengue transmission vector. First, its eggs can survive desiccation and colder temperatures for extended periods of time, making control efforts difficult. The genus is also highly anthropophillic, and is capable of feeding on more than one person. This trait leads to the common result of several members of a household becoming infected, from a single mosquito, in a 24 hour period. Aedes aegypti females will generally not bite at night, except in lit areas. Dispersal of adult biting (female) mosquitos is often within 100 meters of their birth. However, they have been known to travel over 400 meters in search of oviposition sites, or many miles through passive transportation (such as cars or planes).[7]

Aedes aegypti mosquitos receive the Dengue virus by biting humans who are infected. This transmission is possible several days before any human symptoms appear, and for another five days after the appearance of fever. During the subsequent 10-12 day incubation period, the disease spreads from the mosquito's gut back to its salivary glands. Once there, the virus will be passed to humans through female mosquito bites.

(c) Cape Verde

Cape Verde is an archipelago nation consisting of 10 islands, approximately 570 kilometers off the coast of Senegal, Africa. The climate is diverse across the islands, ranging from dessert to rainforest. Average peak daily temperatures in the capital city of Praia (on the island of Santiago) range from 25°-29° C, with yearly rainfall there of around 26.1cm.[8] The climate also varies greatly even across the same island. For example, Santiago (the most populous island) is quite arid on its southern and southwestern coasts. Other regions, however, receive substantial rainfall from the ocean and mountains and are covered in rainforests.[9]

(d) Outbreak

In October 2009, the Cape Verde Ministry of Health announced that a Dengue outbreak – the first recorded in the nation's history – had been discovered on the island of Santiago.[10] In just over two months, the virus spread to at least five islands and resulted in 21,137 cases of Dengue Fever, 174 cases of Dengue Hemorrhagic Fever, and 4 deaths. Of these 21,315 combined cases, 14,579 (14742 DF, 87 DHF, and all four deaths) occurred in the capital of Praia, on the island of Santiago. [11] Perhaps due the lack of native immunity in the Cape Verde population, the virus spread at an unusually high rate – peaking at over 1,000 new cases per day in late October. The serotype behind the outbreak was identified as DENV-3 by the Pasteur Institute in Darkar, Senegal.[12]

This Cape Verde epidemic was chosen to study for this paper because it presents a valuable opportunity to study the behavior of the Dengue virus without the added complexity of immunity, increased susceptibility, or multiple serotypes. Often, studies published on Dengue circumvent this complication and artificially simplify things by choosing to only examine one serotype (ignoring the others), or by looking at a carefully isolated geographic region. However, the 2009 Cape Verde outbreak is simpler naturally, so there is no need to use artificial human data selection or manipulation that could lead to inaccurate results.

3. Obtaining a Data Set

(a) Sources

The initial step in the project was to obtain accurate data about the 2009 epidemic, including the numbers of infections (DF and DHF) throughout the months of the outbreak. However, this proved difficult for a number of reasons. First, since Cape Verde had never recorded a Dengue epidemic before, there initially were little to no resources and systems in place to record data. While the epidemic is believed to have started in early October, the first public acknowledgement of it wasn't until October 23rd. By the 27th, the Cape Verdian government had reported over 3,367 cases and requested help from the World Health Organization. [13] Once the epidemic was acknowledged, infection counts from the Ministry of Health came intermittently, primarily through second-hand sources such as Jornal de Notícias (News Journal) and ASemana (The Weekly). Thus, reports were both delayed and sporadic.

Additionally, a thorough search of the literature revealed no published record of regularly sampled data from during the epidemic – either daily or weekly counts. So, data for this study was instead compiled from extensive internet research. The terms "Dengue", "Cape Verde", and "Cabo Verde" were chronologically searched for – in English, Spanish and Portuguese – using one-week intervals from September 1st 2009 to the end of December 2009. Any speculative or uncited counts from newspapers, etc. were

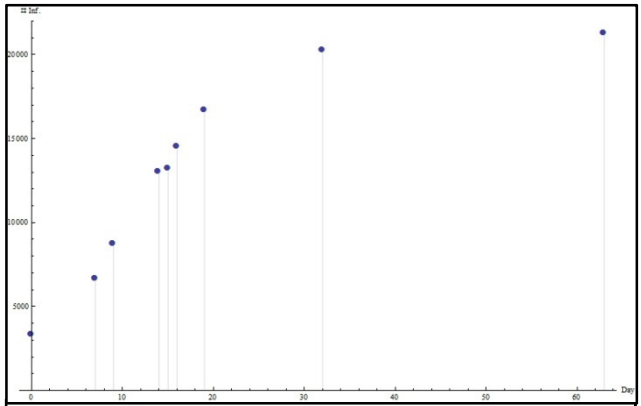

Figure 2 - Number of Infections vs. Time (in days)

discarded. In total, nine official counts, from either the Ministry of Health or WHO, were obtained from throughout the epidemic. These can be seen plotted in Figure 2.

(b) Addressing issues with data set

In order to effectively study this epidemic, or attempt to fit a mathematical model to it, more data points are needed. Curve fitting is one method commonly used in such situations. Since the Cape Verde epidemic infection counts appeared of logistic type, and such behavior is common with viruses, a logistic curve fit was attempted. Such a curve can be described by the equation

Day	# Infected
0	3367
7	6707
9	8799
14	13068
15	13280
16	14564
19	16744
32	20321
63	21311

Table 1 - Known Data Points

$$I = \frac{L}{1+e^{\beta_0+\beta_1 t}} \qquad (1)$$

where I is the number of infected at time t, L is the carrying capacity (upper limit) of the population, and β_0 and β_1 are variables that effect the shape and orientation of the logistic curve.[14] The nine known data points (Table 1) were used to derive values of $\beta_0 = 1.72027$ and $\beta_1 = -0.152034$. The value of carrying capacity was chosen as $L = 21{,}319$ using a combination of standard fitting techniques and visual inspection, as well as to minimize error across the nine points. The resulting logistic equation, fitted for the specific data from this Cape Verdean epidemic, is

$$I = \frac{21{,}319}{1+e^{1.72027-0.152034t}} \qquad (2)$$

Here, the validity of this fit is tested by two methods. First, the theoretical curve fit equation is plotted along with the nine actual points (Figure 3) to allow visual comparison. Then the predicted and theoretical values for each of the nine data points are compared, and a percent error computed for each. The average error for the nine points is 2.44%, indicating that the proposed logistic fit offers approximately 97.56% accuracy. This continuous, theoretical data set, based on the obtained real-life values, can then be used to extrapolate the number of infected humans at any point in time, *t*, in the Cape Verde epidemic.

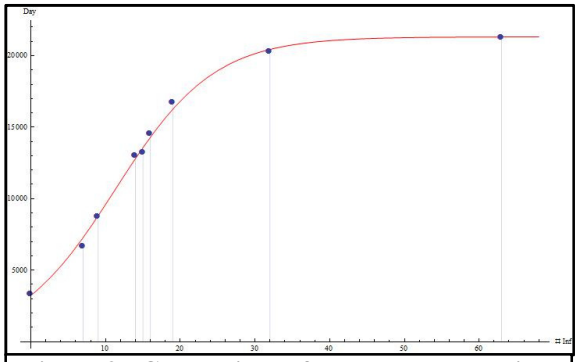

Figure 3 - Comparison of Real and Theoretical Data

4. Selection of a Mathematical Model

(a) Introduction of system

Many different methods currently exist for mathematically modeling Dengue – at least 37 as of 2006. [15] However, in this paper the choice was made to use a model proposed by Pinho et. Al. in 2010. [16] This decision was made for several reasons. First, while many of the existing models are poorly presented or explained, the Pinho one is introduced rigorously. Secondly,

derivations are carefully done out, either in the text or appendixes. Finally, the proposed model is actually tested on real world data – and on a region of particular interest for our study.

The Pinho model is a system of seven differential equations. The model includes four human classes: Susceptible, Exposed, Infected, and Recovered (SEIR) – although these can be simplified to three. Additionally, it recognizes four groups of mosquitos: Aquatic, Susceptible, Exposed, and Infected. The seven corresponding differential equations, four for mosquitos and three for humans, are:

$$
\begin{aligned}
\frac{dA}{dt} &= k\delta(t)\left(1-\left(\frac{A}{C}\right)\right)M - \big(\gamma_m(t)+\mu_a(t)+c_a(t)\big)A \\
\frac{dM_s}{dt} &= \gamma_m(t)A - \frac{b\beta_m M_s H_i}{H} - \big(\mu_m(t)+c_m(t)\big)M_s \\
\frac{dM_e}{dt} &= \frac{b\beta_m M_s H_i}{H} - \big(\theta_m(t)+\mu_m(t)+c_m(t)\big)M_e \qquad (3) \\
\frac{dM_i}{dt} &= \theta_m(t)M_e - (\mu_m(t)+c_m(t))\,M_i \\
\frac{dH_s}{dt} &= \mu_h(H-H_s) - \frac{b\beta_m H_s M_i}{H} \\
\frac{dH_e}{dt} &= \frac{b\beta_m H_s M_i}{H} - (\theta_h+\mu_h)\,H_e \\
\frac{dH_i}{dt} &= \theta_h H_e - (\alpha_h+\mu_h)H_i
\end{aligned}
$$

A, M_s, M_e, and M_i represent the number of mosquitos in the aquatic, susceptible, exposed and infected mosquitos, respectively, while H_s, H_e and H_i are for the susceptible, exposed and infected human classes.

The method by which this model was constructed, and various other justifications about its characteristics, are described in two 2009 papers by the Yang, et. Al.[17] [18] These equations allow predictions of how the various groups of humans and mosquitos will change, based on various parameters and conditions. The parameters, and the method for obtaining their values for the Cape Verde epidemic, are explained in the following section.

(b) Method for obtaining parameter values

Obtaining values directly for the various parameters in the 2009 Cape Verde epidemic is nearly impossible because no published data exists for those environmental and biological variables prior to the outbreak. Instead, values from other regions with similar environmental conditions and better data repositories can be substituted – provided the choice for substitution is judiciously made and carefully justified.

In the Pinho paper, parameters (Table 2) were chosen to fit two particular epidemics that occurred in the Brazilian city of Salvador, Bahia in 1995-1996 and 2002, respectively. Further explanation of these parameter values can be found in their paper and in the cited sources. The decision to base parameter values for this paper modeling Cape Verde off of those from Salvador, Bahia was based on several factors.

First, the average temperature range during the warm and rainy season of Praia, Cape Verde (where the brunt of the epidemic occurred) is similar to that of the Brazilian city: 24.0° - 28.25° for Praia and 23.0°-30.0° C for Salvador. Comparison of precipitation is more complicated. A total of approximately 24.2cm falls, on average, during Praia's wettest three months while 63cm typically falls during the wet season of Salvador. However, in September of 2009, Cape Verde was hit with unusual rainfall (Figure 4 and 5), the result of an easterly wave that resulted in torrential rainfall for several days. On September 18th, 2009, the island of Santiago, Cape Verde (on which Praia is located) received approximately 10.8cm of rainfall in a single day.[19] Thus, while Praia, the center of the Cape Verde epidemic, is generally more dry than Santiago, in October 2009, shortly after this large rainfall, the standing water and dampness (both important for Aedes Aegypti to thrive) in Praia would have been equal if not greater.

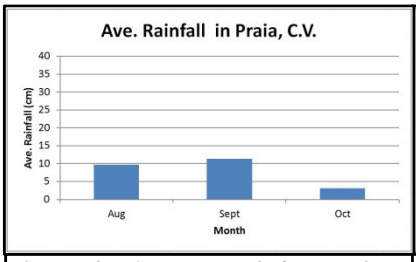

Figure 4 – Average rainfall during the Cape Verde wet season

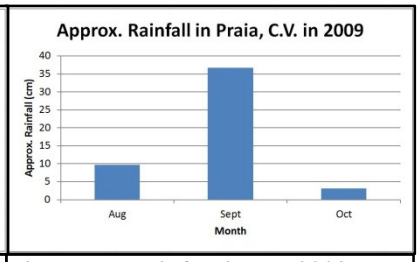

Figure 5 - Rainfall in the 2009 Cape Verde wet season

Parameter	Biologic Meaning	Range
δ	Average oviposition rate	0-11.2 per day
μ_m	Average mosquito mortality rate	0.02-0.09 per day
μ_a	Average aquatic mortality rate	0.01-0.47 per day
γ_m	Average aquatic transition rate	0-0.19 per day
θ_m	Extrinsic incubation	0.02-0.2 per day
μ_h	Human mortality rate	0.0143-0.0167 per year
θ_h	Intrinsic incubation rate	0.083-0.17 per day
α_h	Recovering rate	0.083-0.25 per day
k	Fraction of female mosquitos hatched from all eggs	0-1
C	Mosquito Carrying Capacity	-
b	Average bite per mosquito per day	0-1
β_m and β_m	Effective contact rates	0.75
c_a and c_m	Control effort rates	0-1

Table 2 - Pinho Parameter Values

The values used in the Pinho paper, taken from Salvador, Brazil, can be seen in Table 2. Control efforts in Cape Verde are considered to be 0 since a Dengue epidemic had never occurred before and no control programs were in place. The mosquito carrying capacity, C, is a crucial parameter. However, neither the Pinho study nor the many other studies reviewed while writing this paper gave an actual, numerical value for C. We propose a solution to this difficulty in the following two sections.

5. Computation of Λ

(a) Purpose and Method

In epidemiology, Λ is defined as the force of infection. The force of infection is a measure of the risk of a susceptible person to become infected, per unit time.[20] Pinho et. Al. (2010) demonstrated that, for small values of t (near the beginning of an epidemic), Λ can be related to the total number of people infected, I, by the equation

$$I \approx \exp(\Lambda t) \qquad (4)$$

However, earlier in our paper it was shown that the number of infected at a given time can also be estimated accurately using a logistic fit. It can thus be further shown that

$$I = \frac{L}{1+e^{\beta_0+\beta_1 t}} \approx \exp(-\beta_1 t), for\ small\ t \qquad (5)$$

Visual and statistical comparisions of the logistic and exponential equations are shown in Figure 6 and Table 4, below. From *(4)* and *(5)* it can be seen that $\Lambda = -\beta_1 = 0.152034$.

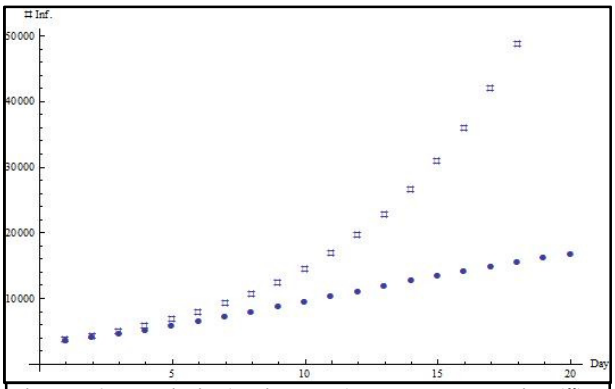

Figure 6 - Logistic (Thick Dot) and Exponential (#) Plotted Together vs. Time

Day	Actual Logistic Fit	Approximation	% Error
1	3676.858	3676.544	0.009
2	4162.714	4280.234	2.823
3	4695.682	4983.050	6.120
4	5275.904	5801.268	9.958
5	5902.364	6753.838	14.426
6	6572.735	7862.820	19.628
7	7283.274	9153.897	25.684
8	8028.804	10656.969	32.734
9	8802.786	12406.847	40.942
10	9597.499	14444.054	50.498

Table 4 - Percent Error between Logistic Fit and Exponential Approximation

6. Computation of R_0 and C Values

(a) Purpose

In epidemiology, the variable R_0 is defined as the "basic reproductive number", and is the number of cases generated by one case during its infective stage. This single variable can serve as a highly useful approximation of an epidemic's behavior.[21] For example, for a $R_0 < 1$ an epidemic will naturally die out while, for $R_0 > 1$ it will continue to spread. Thus, one goal in battling infectious diseases is to decipher what combination of parameters (control efforts, etc.) will result in an epidemic naturally dying out. Each disease has a range of R_0 values that are typical of its epidemics. For example, the common flu has a R_0 of approximately 1.2, HIV/AIDS of 2-5, and Measles of 12-18.[22] [23] Dengue's basic reproductive number can range, but most studies have estimated it between 1.15 and 3.00.[24] Pinho et. Al (2010) estimate the R_0 value for the Salvador epidemic at 2.85. The basic reproductive number, once known, can also be used to work backwards and solve for other epidemic parameters.

(b) Method

To solve for the R_0 value of the 2009 Cape Verde epidemic, we use the following equation from Pinho, et. Al (2010).[25]

$$R_0^2 = \left(\frac{\Lambda}{\theta_m+\mu_m+c_m}+1\right)\left(\frac{\Lambda}{\theta_h+\mu_h}+1\right)\left(\frac{\Lambda}{\theta_m+c_m}+1\right)\left(\frac{\Lambda}{\alpha_h+\mu_h}+1\right) \qquad (6)$$

In this case, Λ is already solved for, c_m is 0 (no control), and simple averages of the other five variables' ranges are used. (See Table 2 for these ranges.)

(c) Results

Substituting these values of Λ, c_m, and other previously explained parameter values into *(6)* results in an average basic reproductive number for the 2009 Cape Verde epidemic of R_0 = 5.52. This value is slightly above the normal Dengue epidemic R_0 range of 1.15 – 3.00. However, the Cape Verde outbreak was unusually virulent. While most Dengue epidemics peak below 200 new cases per day, this one reached approximately 1,000 per day at the peak, in late October. So, a value of 5.52 for Cape Verde appears reasonable.

(d) Solving for C

Finally, once the force of infection and reproductive number are computed, it is possible to use another equation from the paper by Pinho et. Al. (2010) to work backwards and solve for C. This equation is

$$R_0 = \sqrt{\frac{C\gamma_m\theta_h\theta_m b^2\beta_h\beta_m}{H(\theta_h+\mu_h)(\theta_m+\mu_m+c_m)(\alpha_h+\mu_h)(\mu_m+c_m)^2}\left(1-\frac{1}{R_m}\right)} \qquad (7)$$

Where R_m, the basic offspring of the mosquitos, is defined as

$$R_m = \frac{k\delta\gamma_m}{(\mu_m+c_m)(\gamma_m+\mu_a+c_a)} \qquad (8)$$

Using *(7)* and *(8)*, the various known parameters, and a Cape Verde population, *H*, of 496,000[26], *C* can be solved for algebraically. The result is a computed carrying capacity for Cape Verde, at the start of the 2009 epidemic, of $C = 0.918455$.

7. Direct Comparison of Predicted and Actual Infections

The model of Pinho et. Al (2010) was implemented in Mathematica and a series of simulations was run using the range of parameter values either described by Yang et. Al (2009) or derived in the present paper. Our goal was to compare the output of this model with the data from our logistic fit. We found that various combinations of parameter values, chosen from within allowed ranges, resulted in a model output that was consistent with the actual data (see Figure 7). Specifically, both the peak number of infections per day and the time at which this occurs are predicted very well by the model. Further work is needed to more rigorously investigate the sensitivity of the model output to variations in system parameters. However, this is left for a later study.

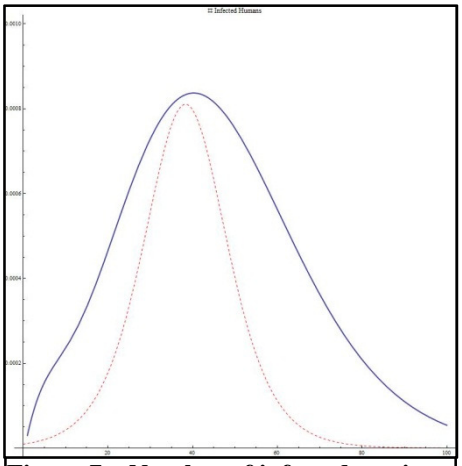

Figure 7 – Number of infected vs. time, computed by logistic fit (dashed) and Pinho model (solid)

8. Conclusions

Today, nearly half of the world population is at risk for contracting the Dengue virus. While most often not fatal, it causes a variety of moderately to extremely unpleasant symptoms.

Treating and coping with the disease also results in billions of dollars a year in costs – over $38 million a year in the US territory of Puerto Rico alone, for example. However, it is estimated that each $1 US spent on prevention saves $5 in illness-related costs. [27] Given this, and the lack of current Dengue vaccine or definitive "cure", there is great interest in prevention and understanding.

Mathematical models are one invaluable tool towards achieving both these goals. Once selected and carefully prepared with parameter values etc, a model such as that used in this paper can be a powerful device. For example, a test to see the effect of changing a parameter value (increasing the amount of mosquito larvae controls, such as pesticide spraying, perhaps) that would take weeks or months in real life can be accomplished with a model in a matter of minutes. Thus, using mathematical models in medicine and epidemiology can save time, resources and money – things all particularly scarce in many of the countries where Dengue causes the most damage. However, creating these models can be quite difficult – especially for a disease as complex as Dengue. While many papers rely on artificial simplification or selection, choosing a virgin environmental, such as Cape Verde, results in a variety of natural simplifications that can make modeling and studying Dengue less difficult.

This paper applied an existing model, proposed by Pinho et. Al in 2010, to a different epidemic with similar geographic and meteorological characteristics. In the process of doing so, the force of infection, Λ, was computed in a novel way – based on an observed relation for small values of t. We generated our dataset using the logistic fit method. This method is commonly used in various branches of biology, but not in any of the many previously published Dengue papers we reviewed during this study. Ultimately, the model gave a reasonable R_0 value and generated theoretical data that was consistent with expectations. This indicates that the Pinho model can be used to model Dengue in regions of the world other than Brazil.

On a final note, our simulations for the 2009 Cape Verde epidemic suggest that reducing the oviposition rate, δ, and the number of exposed humans, H_e , in the model has a profound effect on decreasing the number of infected people at any given time during the epidemic. This is encouraging, as each of these parameters can be reduced through relatively inexpensive means such as public education, reduction of standing water, and use of mosquito nets.

While the mathematical modeling of Dengue is highly useful, significant work is needed in improving the precision and accuracy of these tools. Additionally, collaborative work between physicians, pharmaceutical researchers, biologists, epidemiologists, and others is crucial if Dengue is to be successfully combated, or ever defeated.

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However, I am most grateful to him for showing me how powerful and beautiful a tool mathematics can be in biology and medicine – information I hope to apply in medical school and beyond.

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