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# **Temporal Trends and Regional Variability of 2001-2002**

## **DENV-3 Epidemic in Havana City: Did Hurricane Michelle**

### **Contribute to its Severity?**

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## **Abstract**

### **Background**

In 2001, dengue transmission was detected in Havana City where 12,889 cases, mostly of DENV-3 type, were reported with 78 DHF cases and 3 deaths due to Dengue

### **Methodology/Principal Findings**

A simple mathematical model, the Richards model, is utilized to investigate the temporal progression of the epidemic in 14 municipalities in Havana City and to quantify the transmissibility of the epidemic via the basic reproduction number  $R_0$ . Model fits using weekly reported dengue case data for each of the municipalities as well as for all of Havana City indicate either a 2-wave or 3-wave outbreak. Estimates for  $R_0$  vary from 1.97, 95% CI: (1.94, 2.01), for Arroyo Naranjo to 61.06 (60.44, 61.68) for Boyeros.

### **Conclusions/Significance**

Wide regional variability in our estimates of  $R_0$  for dengue is consistent with reported values in literature from various regions of the world, most likely due to heterogeneity in community structure, community-wide pre-immunity, geographical locations, and social networking. By case reporting week, the dengue epidemic in Havana had started to go down initially around weeks 20-22 (first turning point/peak incidence). However, infections spread once again after week 24, perhaps due to Hurricane Michelle, one of the most destructive and wettest tropical cyclones ever in Cuba that may have contributed to a protracted and more severe epidemic. For all municipalities with 3-wave, model fit indicates a new third wave occurred after Christmas/New Year in weeks 31-32, likely attributable to a decrease in reporting due to reluctance for hospital visits during the holidays. Our result illustrates the potential impact of climatological

events on disease spread. It further highlights the need to be well-prepared for possible worsening disease spread in the aftermath of natural disasters such as hurricanes/typhoons.

**Keywords:** Dengue; Cuba; DENV-3; mathematical model; basic reproduction number; turning point; Hurricane Michelle.

## **Author Summary**

The 2001-2002 DENV-3 epidemic in Havana City lasted almost 7 months with more than 10,000 cases, 78 DHF cases, and 3 deaths. One of the turning point of the multi-wave epidemic coincided with the occurrence of Hurricane Michelle, one of the most destructive and wettest tropical cyclones ever in Cuba that may have contributed to a protracted and more severe epidemic. Estimate of the basic reproduction number  $R_0$  for each municipality reveals wide regional variability exhibited which is consistent with reported values of  $R_0$  for dengue in literature in various regions of the world. Interestingly, for some municipalities with 3 waves, the start of the third wave coincided with the end of the Christmas/New Year holiday, possibly attributable to decrease reporting during the holidays. Our result illustrates the potential impact of climatological events on disease spread. It further highlights the need for health community to be aware and better prepared for the possibility of a worsening disease spread in the aftermath of natural disasters such as hurricanes/typhoons.

## **Introduction**

Dengue virus infection in humans causes a spectrum of illness ranging from asymptomatic or mild febrile illness to severe and fatal hemorrhagic disease. Infection with any of the four known serotypes of Dengue (DENV-1, DENV-2, DENV-3, and DENV-4) causes a similar clinical presentation that may vary in severity, depending on the strain and serotype of the infecting virus and the immune status, age, and genetic background of the human host. Due to its wide spread and multiple serotypes, the disease, even in absence of fatal forms, produces significant economic and social costs in terms of absenteeism, immobilization, debilitation, medication, and death).

In Cuba, Dengue viruses are transmitted by the *Aedes aegypti* mosquito. The mosquito is characterized by its biting pattern, which consists of multiple blood meals during each egg-laying cycle, and its ability to grow in water reservoir during of its immature stages (i.e., egg, larva and pupa). These features make it an ideal vector for dengue virus transmission, especially in large urban areas where the human population density is high with abundant artificial containers in where the aquatic stages of *Aedes aegypti* flourish [1]. *Aedes aegypti* is infected by sucking infected human blood, while humans are infected with dengue viruses when bitten by an infective mosquito. The global spread of dengue can be directly attributable to the proliferation and adaptation of mosquitoes.

Currently the only way to control and reduce dengue transmission is to implement alternative strategies such as: (i) reduction of vector populations in both the adult (by fumigation and/or by other chemical/biological treatments [2]) and the immature stages (by eliminating breeding sites); (ii) early detection of infected humans to prevent the virus transmission to susceptible mosquitoes. In Cuba the rainy season (lasting 6 months from May to October) produces a proliferation of mosquito

populations which includes *Aedes aegypti*. This persistent presence of *Aedes aegypti*, together with the increased international arrivals from dengue-endemic countries in recent years, has led to several outbreaks including a major 2001 outbreak in Havana City [3].

In the Caribbean region the first major outbreaks of dengue fever (with a significant number of severe cases) occurred in Cuba in 1977 (with DENV-1) and in 1981 (with DENV-2). Both epidemics affected the entire country, producing more than 500,000 and 300,000 dengue cases, respectively. In 2000, a minor outbreak of dengue was detected in Havana City with 138 cases of DF, when DENV-3 and DENV-4 viruses were isolated. In 2001, dengue transmission was detected in Havana City where 12,889 cases, mostly of DENV-3 type, were reported with 78 DHF cases and 3 deaths due to Dengue [3].

To ascertain how did this epidemic come to pass, we will employ a simple mathematical model, the Richards model, to investigate the temporal progression of the epidemic in various municipalities in Havana City and to quantify the transmissibility of the epidemic via the basic reproduction number  $R_0$ .

## **Methods and Materials**

### **Data**

The 2001-2002 dengue outbreak data, by reporting week, for each of the 15 municipalities in Havana City are obtained from the Pedro Koury Tropical Medicine Institute (IPK) in Havana, Cuba, which spans from May 30, 2001 to February 27, 2002. We designate the first calendar week (Sunday to Saturday) with reported case in Playa, from May 27 to June 2, 2001, as week 1 of our data. Subsequently the data spans 40 weeks, with week 40 covering February 24-March 2, 2002.

### **The Richards model**



We fit the data to the Richards model [4]: where  $C(t)$  is the cumulative number of cases reported at time  $t$  (in weeks). Here the prime “'” denotes the rate of change with respect to time. The model parameter  $K$  is the maximum case number (or final outbreak size) over a single phase of outbreak,  $r$  is the per capita growth rate of the infected population, and  $a$  is the exponent of deviation. The solution of the Richards model is  $C(t) = K / (1 + \exp(-r(t - t_i)))^a$ , where  $t_i$  is the turning point of the epidemic (or the inflection point of the cumulative case curve) and  $\ln$  denotes the natural logarithm. Using the Richard model, we can directly fit empirical data from a cumulative epidemic curve to obtain estimates of epidemiological meaningful parameters, including the growth rate  $r$ .

In such a model formulation, the basic reproduction number  $R_0$  is given by the formula  $R_0 = rT$ , where  $T$  is the disease generation time defined as the average time interval from infection of an individual to infection of his or her contacts. It has been shown mathematically that, given the growth rate  $r$ , the equation  $R_0 = rT$  provides the upper bound of the basic reproduction number regardless of the distribution of the generation interval used [5]. Additional technical details regarding the Richards model can be found in [6-8].

The turning point or inflection point  $t_i$  of the cumulative case data, defined as the time when the rate of case accumulation changes from increasing to decreasing (or vice versa) can be easily pinpointed as the point where the rate of change transitions from positive to negative; i.e., the moment at which the trajectory begins to decline. For epidemics with two or more phases, a variation of the S-shaped Richards model has been proposed [7]. This multi-staged Richards model distinguishes between two types of turning points: the initial S-Shaped cumulative case curve which signifies the first turning point that ends initial exponential growth, or simply the time where peak incidence of a wave of cases occurs; and a second type of turning point in the

cumulative epidemic curve where the growth rate of the number of cumulative cases begins to increase again, signifying the beginning of the next wave. This variant of Richards model provides a systematic method of determining whether an outbreak is single- or multi-phase in nature, and can be used to distinguish true turning points from peaks and valleys resulting from random variability in case counts. Readers are also referred to [9, 10] for its applications to dengue, and to [11-14] for applications to 2009 H1N1. Model parameter estimates based on the explicit solution of the Richards model can be obtained easily and efficiently using any standard software with a least-squares approximation tool, such as SAS or Matlab.

## Results

The results of the best Richards model fit for 14 of 15 municipalities in Havana City, with estimates for  $t_i$ ,  $r$ ,  $K$ ,  $R_0$  and their respective 95% confidence intervals (CI), are listed in Table 1. The municipality of Cotorro had only 34 reported cases scattered over 20 weeks and therefore cannot be fitted. We also fitted the combined total case data of all 15 municipalities in Havana City including Cotorro (see Table 1b), for the purpose of comparison. Note that the week in which the true turning point for each wave occurred is  $t_i$  weeks (3<sup>rd</sup> column in the tables) after the first week of the wave, rounding off to the next integer week. For example, the turning points for the three waves in Playa occurred in weeks 18 (3+14.3 in the first row of Table 1a), 25 (22+2.46), and 35 (30+4.38), respectively.

The model fits for the most severely affected municipalities, namely Playa (with the first reported case of this epidemic), Plaza, Central Havana, and Old Havana, as well as for all 15 municipalities of Havana City, are given in Figure 1.

All model fits indicate a 2-wave or 3-wave outbreak for each of the 14

municipalities as well as for all of Havana City. Outbreaks in Old Havana, Regla, and Guanabacoa only are 2-wave, while all other municipalities exhibit 3-wave outbreaks. For the purpose of comparing regional heterogeneity, we also provide timeline graphs of the 14 fitted municipalities in Figure 2.

## **Conclusions and Discussion**

Previous large dengue epidemics in Cuba were associated with DENV-1 (in 1977) and DENV-2 (in 1981). More recently, two smaller dengue outbreaks were reported in 1997 (DENV-2) and September 2000 (DENV-3 and DENV-4) [3]. Subsequently, there was very little pre-existing immunity among the population in Havana for this 2001-2002 DENV-3 epidemic, although some cases of DHF/DSS might have occurred in persons infected with DENV-3 in a background of immunity to DENV-1 and DENV-2 from either the 1981 epidemic or dengue epidemics during or before the 1940s [15]. Table 1 indicate that the estimates for  $R_0$  in the initial wave vary from 1.974 (95% CI: 1.941, 2.006) for Arroyo Naranjo to 61.062 (60.444, 61.680) for Boyeros, with high disease transmissibility (large  $R_0$ ) in the initial wave, followed by succeeding waves with smaller  $R_0$ . The wide regional variability exhibited in our estimates is consistent with other reported values of  $R_0$  for dengue in literature in various regions of the world (see, e.g., [16] or Table 2 in [10]), most likely due to heterogeneity in community structure, community-wide pre-immunity, geographical locations, and social networking.

Moreover, there is also a clear regional heterogeneity in the temporal trend, where Old Havana, Regla, and Guanabacoa are 2-waved while the other municipalities are 3-waved. Even Central and Old Havana, which are closely nearby, are fitted different with Central Havana have an additional wave occurring on week 31. However, there are also sample similarities.

Except for Playa, Regla, and Guanabacoa (the latter 2 regions with late outbreaks having the first cases reported in September), all other municipalities as well as all of Havana City had a first turning point (peak incidence) during weeks 20-22 indicating a downturn of cases, regardless whether the data fit exhibits a 2-wave or 3-wave outbreak. Moreover, with the exception of Arroyo Naranjo, Regla, and Guanabacoa, all other municipalities as well as all of Havana City has a turning point of second type around weeks 22-24 that signals an increase in case number and the beginning of a new wave of cases, regardless whether it has a 2-wave or 3-wave outbreak. Interestingly, all 14 municipalities had a turning point (peak incidence) during weeks 25-30, regardless of the number of waves or the timing of initial outbreak. Finally, for all 11 municipalities with 3 waves, the third wave started around weeks 30-32. The last turning point (peak incidence), or a downturn toward the end of the outbreak, came during weeks 33-36 for all municipalities except Old Havana which had a 2-wave outbreak.

More significantly is the underlying cause of this multi-wave epidemic. For the first wave, we note that Hurricane Michelle, the most destructive hurricane in the history of Cuba based on its actual damage [17], struck Cuba on November 4, 2001, the first day of week 24 in our study. Landing on the coast of western and southern Cuba, Michelle was one of the wettest tropical cyclones ever in Cuba [18], produced 4–5 foot waves along with a heavy storm surge. Rainfall amounting up to 754 mm was recorded across the island [19]. Previous studies (e.g., [10], [20], [21]) have proposed that extreme weather conditions, such as typhoon or hurricane which brings substantial amount of precipitation, can be shown to be significantly correlated to the occurrence of a wave of reported dengue cases with a lag of several weeks. The typhoon/hurricane first brings a sudden drop in temperature causing mosquito inactivity and decreased

biting/infection, the ensuing heavy rainfall then leads to increased breeding reservoir for the larvae to proliferate. It is hence conceivable that Hurricane Michelle had contributed to, if not actually causing, the new wave of cases in these municipalities after week 24. In other words, the dengue epidemic in Havana had started to go down initially around weeks 20-22 (first turning point/peak incidence), but spread once again after week 24 after Hurricane Michelle, causing a more severe and longer-lasting epidemic. We note that, since the case data is by reporting week, there is a delay of around one week from actual infections to reporting, mainly due to intrinsic dengue incubation period of 4-7 days.

After a downturn (peak incidence) around weeks 25-30, a new turning point (of second type) for start of a third wave after weeks 30-32 for all 11 municipalities with 3-wave fit (excluding Old Havana, Regla, and Guanabacoa) is also interesting since Christmas and New Year happened to fall on, respectively, weeks 31 and 32. However, the new wave of reported cases is likely attributable to a decrease in reporting due to reluctance on the part of some ill persons for hospital visits during the holidays. Our result illustrates the potential impact of climatological events on disease spread. It further highlights the need for health community to be aware and better prepared for the possibility of a worsening disease spread in the aftermath of natural disasters such as hurricanes/typhoons.

During the 1981 dengue epidemic, the Cuban health authorities started a National Program for Eradication of *Aedes aegypti* which has continued to the present. The campaign was based on the principles of dengue control established by the Pan American Health Organization (PAHO) Guidelines [22] with the involvement of the whole community (governmental and political bodies at all levels, householders, community organizations, etc.), where thousands of workers were mobilized with the

task of periodic inspection of housing, detection and elimination of breeding points for the vector, chemical control of mosquitoes, and an educational campaign. These activities were carried out regularly and reinforced whenever cases of dengue are detected. The 2001 epidemic was no exception ([3]), which may have contributed to the 2001 epidemic being less severe than the previous epidemics in 1977 and 1981. Community-wide cross pre-immunity from earlier epidemics may also have played a role, which is however difficult to gauge without sizable serologic dataset.

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### **Conflict of Interest**

We declare that we have no competing interest.

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### **Author Contributions**

Conceived and designed the experiments: YHH HaD RL. Data acquisition and management: HaD RL. Analyzed the data: YHH. Wrote the paper: YHH HaD.

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## **Figure Legends**

Figure 1. Richards model fit for 2001 dengue outbreak in (1a) Playa, (1b) Plaza, (1c) Central Havana, (1d) Old Havana, and (1e) all of Havana City.

Figure 2. Timelines for 2001 dengue outbreak (with turning points) in: (2a) Playa, Plaza, Central Havana, Old Havana; (2b) Diez de Octubre, Cerro, Marianao, Lisa, Boyeros, and Arroyo Naranjo; (2c) Regla, Havana de Este, Guanabacoa, SMP, and Havana City total.

Table 1a. Estimated Richards model parameters values with 95% confidence intervals (in parenthesis) for all regions other than Regla, Habana de Este, Guanabacoa, Arroyo Naranjo, SMP, and Cotorro. Note that the week in which the true turning point for each wave occurred is  $t_i$  weeks after the first week of the wave.

<b>Region</b>	<b>Week</b>	<b>Turning point <math>t_i</math></b>	<b>Growth rate <math>r</math></b>	<b>Case number <math>K</math></b>	<b><math>R_0</math></b>
Playa	3 - 22	14.30 (13.99, 14.61)	0.393 (0.364, 0.422)	1601 (1564, 1638)	3.848 (3.821, 3.874)
	22 - 30	2.46 (1.26, 3.66)	0.019 (0.014, 0.023)	1764 (1706, 1822)	1.066 (1.062, 1.069)
	30 - 37	4.38 (4.14, 4.62)	0.274 (0.247, 0.301)	79 (76, 81)	2.558 (2.539, 2.557)
Plaza	12 - 23	7.72 (7.16, 8.27)	0.660 (0.145, 1.175)	845 (627, 1064)	9.611 (9.172, 10.049)
	23 - 32	3.76 (3.21, 4.30)	0.106 (0.092, 0.119)	1389 (1336, 1442)	1.436 (1.426, 1.447)
	32 - 39	1.80 (1.09, 2.52)	0.025 (0.018, 0.031)	1468 (1459, 1476)	1.088 (1.083, 1.093)
C. Hab	11 - 23	9.78 (8.90, 10.65)	0.747 (0.475, 1.018)	613 (534, 693)	12.937 (12.702, 13.172)
	23 - 31	3.63 (2.29, 4.96)	0.137 (0.093, 0.182)	1366 (1184, 1549)	1.601 (1.306, 1.895)
	31 - 38	2.58 (2.02, 3.15)	0.044 (0.037, 0.052)	1564 (1543, 1585)	1.164 (0.870, 1.458)
Old Havana	12 - 23	8.35 (7.54, 9.16)	0.655 (0.434, 0.876)	167 (151, 184)	9.441 (9.253, 9.628)
	23 - 40	11.68 (11.33, 12.02)	0.122 (0.114, 0.129)	817 (800, 834)	1.518 (1.511, 1.525)
Diez de Octubre	11 - 24	9.90 (9.53, 10.26)	0.327 (0.285, 0.370)	362 (345, 379)	3.070 (3.033, 3.108)
	24 - 31	4.60 (4.11, 5.09)	0.157 (0.133, 0.180)	848 (806, 891)	1.711 (1.694, 1.728)
	31 - 38	2.79 (0.86, 4.73)	0.636 (0.228, 1.043)	119 (109, 129)	8.842 (8.555, 9.130)

Cerro	17 - 22	4.06 (4.03, 4.10)	0.483 (0.470, 0.496)	375 (369, 381)	5.229 (5.223, 5.235)
	22 - 30	2.58 (0.29, 4.87)	0.195 (0.056, 0.335)	850 (763, 937)	1.954 (1.848, 2.060)
	30 - 39	5.92 (4.71, 7.14)	0.030 (0.023, 0.037)	1009 (985, 1033)	1.107 (1.101, 1.112)
Marianao	8 - 23	12.70 (12.60, 12.79)	0.581 (0.556, 0.605)	627 (618, 636)	7.320 (7.298, 7.342)
	23 - 32	1.70 (0.53, 2.87)	0.122 (0.088, 0.156)	1062 (1037, 1088)	1.518 (1.490, 1.545)
	32 - 37	3.38 (2.37, 4.39)	0.028 (0.018, 0.038)	1147 (1130, 1165)	1.100 (1.095, 1.105)
Lisa	13 - 23	7.69 (7.45, 7.94)	0.760 (0.674, 0.847)	249 (241, 257)	13.555 (13.483, 13.627)
	23 - 32	4.40 (3.63, 5.17)	0.081 (0.066, 0.097)	426 (406, 445)	1.322 (1.310, 1.334)
	32 - 38	1.91 (1.06, 2.75)	0.034 (0.023, 0.044)	478 (472, 483)	1.122 (1.116, 1.129)
Boyerros	14 - 23	6.74 (5.07, 8.41)	1.199 (0.428, 1.971)	339 (290, 387)	61.062 (60.444, 61.680)
	23 - 31	2.99 (1.82, 4.17)	0.230 (0.092, 0.367)	896 (766, 1025)	2.197 (2.092, 2.302)
	31 - 39	1.08 (0.09, 2.06)	0.038 (0.029, 0.048)	960 (946, 973)	1.140 (1.133, 1.148)

Table 1b. Estimated Richards model parameters values with 95% confidence intervals (in parenthesis) for Regla, Habana de Este, Guanabacoa, Arroyo Naranjo, and SMP. Note that the week in which the true turning point for each wave occurred is  $t_i$  weeks after the first week of the wave.

<b>Region</b>	<b>Week</b>	<b>Turning point <math>t_i</math></b>	<b>Growth rate <math>r</math></b>	<b>Case number <math>K</math></b>	<b><math>R_0</math></b>
Regla	21 - 31	5.11 (4.38, 5.84)	0.420 (0.181, 0.659)	188 (162, 214)	4.215 (4.017, 4.413)
	31 - 38	1.95 (1.22, 2.68)	0.058 (0.042, 0.075)	208 (206, 211)	1.221 (1.209, 1.233)
Havana del Este	14 - 24	7.71 (4.86, 10.55)	0.841 (0.203, 1.479)	158 (113, 204)	17.882 (17.353, 18.410)
	24 - 31	4.81 (4.60, 5.01)	0.210 (0.196, 0.223)	437 (423,451)	2.052 (2.042, 2.061)
	31 - 39	2.32 (1.43, 3.21)	0.085 (0.062, 0.108)	633 (620, 646)	1.340 (1.322, 1.357)
Guanabacoa	16 - 31	8.81 (8.08, 9.54)	0.490 (0.201, 0.780)	199 (177, 220)	5.373 (5.112, 5.633)
	31 - 37	2.51 (1.18, 3.83)	0.048 (0.029, 0.067)	234 (217, 252)	1.178 (1.166, 1.190)
Arroyo Naranjo	8 - 26	13.05 (12.18, 13.92)	0.198 (0.163, 0.233)	625 (576, 675)	1.974 (1.941, 2.006)
	26 - 31	3.32 (2.82, 3.83)	0.066 (0.055, 0.076)	833 (816, 850)	1.253 (1.248, 1.257)
	31 - 38	3.49 (2.60, 4.38)	0.028 (0.021, 0.035)	954 (941, 968)	1.102 (1.097, 1.106)
SMP	7 - 23	13.30 (12.99, 13.61)	0.460 (0.403, 0.516)	74 (71, 78)	4.836 (4.785, 4.887)
	23 - 31	6.15 (5.60, 6.69)	0.256 (0.209, 0.302)	408 (372, 445)	2.405 (2.369, 2.440)
	31 - 39	4.08 (3.48, 4.67)	0.082 (0.068, 0.097)	616 (603, 629)	1.326 (1.315, 1.337)
Havana City	3 - 23	17.54 (17.43, 17.66)	0.316 (0.305, 0.327)	5933 (5771, 6095)	2.956 (2.945, 2.966)

Total	23 - 31	4.48 (4.14, 4.81)	0.095 (0.087, 0.103)	11003 (10578, 11418)	1.385 (1.379, 1.391)
	31 - 40	3.02 (2.66, 3.37)	0.037 (0.034, 0.041)	12879 (12820, 12938)	1.137 (1.134, 1.140)