MODEL UNCERTAINTY IN THE COMPARISON OF TWO SINGLE DENGUE OUTBREAKS

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ABSTRACT
In recent years, there has been increased interest in using statistical models for analysis of single dengue outbreaks based on the reported cumulative cases. The three parameter logistic (3P logistic) and the Richards models have been used to estimate primary epidemiological parameters in single dengue outbreak. A topic that could be of interest to epidemiologists is the comparison of two single dengue outbreaks based on estimates of key epidemiological parameters: The turning point, the final size and the basic reproductive number R_0. In order to compare two single dengue outbreaks we create a model that takes into account both outbreaks simultaneously. In this paper, we describe different methodologies based on Frequentist and Bayesian approaches that takes into account the model uncertainty in the comparison of two single dengue outbreaks. The Frequentist approach consists of comparing outbreak doing an extension of 3P logistic and Richards models and the use of model averaging for taking into account model uncertainty. In the Bayesian approach, we use a Bayesian hierarchical model and we use Bayesian model averaging applying Gibbs variable selection. The proposed methods are applied to dengue outbreaks that occurred in La Lisa municipality, Havana City, Cuba during 2006 and 2007 outbreaks.

KEYWORDS: Dengue outbreak; parameter estimate; model averaging; Bayesian hierarchical model; Gibbs variable selection.

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RESUMEN
En los últimos años, ha aumentado el interés en el uso de los modelos estadísticos para el análisis de brotes de dengue basado en el reporte de casos acumulados. El modelo logístico de tres parámetros y el modelo de Richards se han utilizado para estimar parámetros epidemiológicos primarios en brotes de dengue. Un aspecto que pudiera interesar a los epidemiólogos es la comparación de dos brotes de dengue de una onda basado en la estimación de parámetros epidemiológicos claves: El acmé, el tamaño final y el número reproductivo básico R_0. Para la comparación se creó un modelo que tiene en cuenta ambos brotes simultáneamente. En este artículo, se describen diferentes metodologías basados en enfoques Frecuentistas y Bayesianos que tienen en cuenta la incertidumbre de modelos. El enfoque Frecuentista consiste en una extensión de los modelos logístico 3P y de Richards y el uso del promedio de modelos para tener en cuenta la incertidumbre. En el enfoque Bayesiano, se utiliza un modelo Bayesiano jerárquico y se utiliza un promedio de modelos Bayesiano aplicando selección Gibbs de variables. Los modelos propuestos son aplicados a los brotes que ocurrieron en el municipio La Lisa, La Habana, durante los brotes del 2006 y 2007.

PALABRAS CLAVES: Brote de dengue; estimación de parámetros; promedio de modelos; modelo jerárquico Bayesiano; selección Gibbs de variables.

1. INTRODUCTION

In recent years, there has been increased interest in using statistical models for analysis of single dengue outbreaks [4] based on the reported cumulative cases. Phenomenological models emphasize the reproducibility of empirical observations using simple models [3]. Maximum likelihood fitting of phenomenological models remains important due to its simplicity and to the difficulty of using modern methods in the context of limited data [9]. A variety of phenomenological models, such as the three parameter logistic model (3P logistic) and Richards model have been developed to model single dengue

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outbreak data based on the reported cumulative cases and to estimate these primary epidemiological parameters [6] [7].
Among the most important epidemiologic parameters are the turning point, i.e. the point in time at which the rate of accumulation changes from increasing to decreasing or the infection point of the logistic (S-shaped) curve in a single epidemic outbreak, the final size of epidemic and the basic reproduction number R_0, defined as the number of secondary infections that arise from a typical primary case in a completely susceptible population [6] [7].
A topic that could be of interest to epidemiologists is the comparison of two single dengue outbreaks based on estimates of key epidemiological parameters. Hypothesized differences in these epidemiological parameters of two single dengue outbreaks can be tested with nonlinear growth models to provide a powerful testing framework.
Recently, we proposed the use of several nonlinear models for estimation and real time-prediction of epidemiological parameters via the model averaging method [12] [13] to take into account the model uncertainty. In this paper, we illustrate different methodologies based on Frequentist and Bayesian approaches that takes into account the model uncertainty in the comparison of two single dengue outbreaks, based on the parameter estimates of the primary epidemiological parameters.
The paper is organized as follows: In the Methods section we present the Frequentist and Bayesian approaches. The Frequentist approach consists of testing outbreak doing an extension of nonlinear model in order to incorporate the two outbreaks in the model, and the use of model averaging for taking account model uncertainty. In the Bayesian approach, a Bayesian hierarchical model using Markov Chain Monte Carlo (MCMC) and Bayesian model averaging applying Gibbs variable selection were used. In the next section Application to the data, the proposed methods are applied to dengue outbreaks that occurred in La Lisa municipality, Havana City, Cuba during 2006 and 2007 outbreaks. Finally, we expose the conclusions.

2. METHODS

2.1 Model uncertainty in the comparison of outbreak: Frequentist approach

Let Y_t a random response, which represents the cumulative number of reported cases at time t.In this study, we consider the assumption that the response (Y_t), are asymptotically normal distributed with mean $\mu(t,\theta)$ and varianceσ^2, e.g. $Y_t \sim N(\mu(t,\theta),\sigma^2)$.
In order to describe the relationship between the cumulative number of reported cases and the time, and to estimate primary epidemiological parameters had been used several nonlinear models. In this case, the mean structure $\mu(t_j,\theta_i)$, is assumed to be the 3P logistic model or Richards model [14]. The 3P logistic model, which can be expressed as follow:

$$\mu(t,\theta) = \frac{\alpha}{1+e^{-\gamma(t-\eta)}} \quad t = 1,\cdots,T$$

where $\theta = (\alpha,\gamma,\eta)$is the parameters vector to be estimated. The α parameter represents the final size of epidemic, γ is the growth rate and η is the turning point of outbreak. The Richards model can be expressed as follow:

$$\frac{\alpha}{[1+k.e^{-\gamma.k.(t-\eta)}]^{\frac{1}{k}}} \quad t = 1,\cdots,T$$

where $\theta = (\alpha,\gamma,\eta,k)$is the parameters vector to be estimated. The parameters α,γ y η are interpreted as in 3P logistic model and k is the exponent of deviation from the standard logistic curve. These two phenomenological models are used since with both models is possible to estimate the most important epidemiological parameter R_0.
For an infection where all secondary infections are exactly equal to the mean generation interval T, the distribution conforms to a so-called delta distribution. It has been shown mathematically that, given the growth rate γ and a generation time with delta distribution T, the equation $R_0 = e^{\gamma T}$ provides the upper bound of the basic reproduction number regardless of the distribution of the generation interval used [6]. To take into account the extrinsic and intrinsic incubation periods as well as the duration of viraemia, we use an

estimated generation time of $T = \frac{24}{7}$ weeks with a range of 16–34 days [7]. The approximate standard errors for the R_0 estimates using the delta method is given for the expression $SE(R_0) \approx T.e^{\gamma T}.SE(\gamma)$, which can be computed with the ESTIMATE statement from NLMIXED procedure in SAS [11]
In order to incorporate the two outbreaks in the model, we define an indicator variable as follow:

$$I_t = \begin{cases} 1 & \text{First outbreak} \\ 0 & \text{Second outbreak} \end{cases}$$

In the case where we consider as mean structure the 3P logistic model, a linear dependence of the model parameters on the outbreak is assumed. The linear dependence of the model parameter can be expressed as follow:

$$\alpha = \alpha_1 + \beta_1.I_t$$
$$\gamma = \gamma_1 + \beta_2.I_t$$
$$\eta = \eta_1 + \beta_3.I_t$$

Where α_1, γ_1 and η_1 are the parameters of the first outbreak. β_1, β_2 y β_3 can be interpreted as the difference between the final size, the growth rate and the turning point among the outbreaks. Similarly, in the case of the Richards model, the linear dependence can be expressed as follow:
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$$\alpha = \alpha_1 + \beta_1.I_t$$
$$\gamma = \gamma_1 + \beta_2.I_t$$
$$\eta = \eta_1 + \beta_3.I_t$$
$$k = k_1 + \beta_4.I_t$$

An advantage of this model is that it allows testing the differences between the key epidemiological parameters of two single dengue outbreak. Formally, for each one of the parameters you can test the hypothesis:

$$H_{0,i}: \beta_i = 0$$
$$H_{1,i}: \beta_i \neq 0$$

To estimate the model parameters it can be used the *gnls* function of R package ***nlme*** [10], which uses as default iterative algorithm, the Broyden-Fletcher-Goldfarb-Shanno (BFGS).

2.2 Model averaging: traditional approach

To the model previously exposed (M_1) certain constraints can be imposed depending on the different combinations with the presence or not of the β_i. As mean structure is the 3P logistic model, we obtain 8 models $M_k,\ k = 1, 2, \ldots, 8$. (See Table 1). In the case, where we consider as mean structure the Richards model we obtain 16 models.

Table 1: Models and constraint when the 3P logistic model is assumed as mean structure.

Models (M_k)	**Constraint**
M_1	-
M_2	$\beta_2 = 0$
M_3	$\beta_3 = 0$
M_4	$\beta_2 = 0, \beta_3 = 0$
M_5	$\beta_1 = 0$
M_6	$\beta_1 = 0, \beta_2 = 0$
M_7	$\beta_1 = 0, \beta_3 = 0$
M_8	$\beta_1 = 0, \beta_2 = 0, \beta_3 = 0$

To carry out model averaging, we fit a set of k candidate models $M_1, M_2, \ldots, M_k$ to the data and to obtain the parameter estimates from all models, $\hat{\theta}_1\hat{\theta}_2, \ldots, \hat{\theta}_k$. The model averaging techniques allow us to estimate the component in θ using information obtained from all fitted models and in that way to account for model uncertainty [5] [8]. It is based upon a weighted average of the parameter of primary interest obtained from different models, giving largest weights to those models that best fit the data [1]. Let us assume that the Akaike's Information Criterion (AIC) is used for model selection. For a given set of k candidate models $M_1, M_2, \ldots, M_k$, Burnham and Anderson [1] proposed to rescale the AIC to

$$\Delta AIC_i = AIC_i - AIC_{min}, \;\; i = 1, \ldots, k$$

Here, AIC_{min} is the smallest AIC value across the set of k models. Burnham and Anderson [1] defined Akaike's weights as

$$w_i(AIC) = \frac{e^{-\frac{1}{2}\Delta AIC_i}}{\sum_{i=1}^{k} e^{-\frac{1}{2}\Delta AIC_i}}$$

Following Burnham and Anderson [1], we can calculate the model averaged estimator for turning point ($\hat{\eta}_{MA}$), the final size of outbreak ($\hat{\alpha}_{MA}$) and the growth rate ($\hat{\gamma}_{MA}$) as follow:

$$\hat{\eta}_{MA} = \sum_{i=1}^{R} w_i(AIC)\hat{\eta}_i \,, \;\; \hat{\alpha}_{MA} = \sum_{i=1}^{R} w_i(AIC)\hat{\alpha}_i \quad \hat{\gamma}_{MA} = \sum_{i=1}^{R} w_i(AIC)\hat{\gamma}_i \quad (5)$$

Here, $\hat{\eta}_i, \hat{\alpha}_i, \hat{\gamma}$ are the parameter estimates for the turning point, final size and the growth rate of any outbreak of *i*-th model, respectively. Note that one can replace the AIC by other information criteria such as BIC, DIC and calculate the model's weight based on these criteria. The estimators for variance for $\hat{\eta}_{MA}$, $\hat{\alpha}_{MA}$ and $\hat{\gamma}_{MA}$ are given, respectively, by:

$$\hat{V}(\hat{\eta}_{MA}) = \left[\sum_{i=1}^{R} w_i(AIC)\sqrt{\hat{V}(\hat{\eta}_i|M_i) + (\hat{\eta}_i - \hat{\eta}_{MA})^2}\right]^2,$$
$$\hat{V}(\hat{\alpha}_{MA}) = \left[\sum_{i=1}^{R} w_i(AIC)\sqrt{\hat{V}(\hat{\alpha}_i|M_i) + (\hat{\alpha}_i - \hat{\alpha}_{MA})^2}\right]^2$$
$$\hat{V}(\hat{\gamma}_{MA}) = \left[\sum_{i=1}^{R} w_i(AIC)\sqrt{\hat{V}(\hat{\gamma}_i|M_i) + (\gamma_i - \hat{\gamma}_{MA})^2}\right]^2$$

2.3 Bayesian hierarchical models

In order to estimate the parameters, the M_k models can be fitted based on Bayesian approach. In this section, a hierarchical Bayesian model is formulated. Let Y_t the cumulative number of reported cases at time t. We assume the following hierarchical normal model for the cumulative number of reported dengue cases. In the first stage of the model, we assume a Normal likelihood,

$$Y_t \sim N(\mu(t,\theta), \tau)$$
$$\mu[t] = \frac{\alpha + \beta_1 . I[t]}{1 + e^{-(\gamma + \beta_2 . I[t]).(t - \eta - \beta_3 . I[t])}}$$

In the second stage of the model, we specify independent non-informative priors for the parameter. The second stage can be expressed as follow:

$$\alpha \sim N(0, \tau_\alpha)$$
$$\gamma \sim N(0, \tau_\gamma)$$
$$\eta \sim N(0, \tau_\eta)$$

To complete the probability model specifications, in the third stage the hyperparameters distribution is assumed as follow:

$$\tau, \tau_\alpha, \tau_\gamma, \tau_\eta \sim gamma(0.001, 0.001)$$

The hierarchical Bayesian model can be fitted using Markov Chain Monte Carlo (MCMC) with the Metropolis-Hastings and Gibbs sampling algorithms implemented in WinBUGS software.
Using the Bayesian hierarchical model, we have a second variant of comparing two single dengue outbreaks taking into account model uncertainty. This variant consists on applying the model averaging technique to the 8 models $M_k,\ k = 1, 2, \ldots, 8$ (or 16 if the Richards model is used) using the deviance information criterion (DIC) for weight´s calculation.

2.4 Bayesian model averaging Gibbs variable selection

A third variant, completely Bayesian, in order to compare two outbreaks taking into account model uncertainty consist on conducting a Bayesian model averaging and compare the results using a simulation technique: Gibbs variable selection (GVS) [2]. Introducing the variable indicator function $g(.)$ reduces the framework to one of fixed dimensionality. We can then utilize standard simulation techniques to estimate $g(.)$ and θ_k for all models, $M_k,\ k = 1, 2, \ldots, 8$. By way of the following framework, Gibbs variable selection (GVS) will be implemented for dataset analysis using WinBUGS. Two cases with different prior distribution are shown.

Likelihood

$$Y[t] \sim N(\mu[t], \tau)$$
$$\mu[t] = \frac{\alpha + g(1).\beta_1.I[t]}{1 + e^{-(\gamma + g(2).\beta_2.I[t]).(t - \eta - g(3).\beta_3.I[t])}}$$

Prior (Case 1)

$$\begin{gathered} g(j) \sim Bernoulli(0.5) \quad j = 1, 2, 3 \\ \alpha \sim N(0, \tau_1), \gamma \sim N(0, \tau_2), \eta \sim N(0, \tau_3) \\ \tau, \tau_1, \tau_2, \tau_3 \sim gamma(0.001, 0.001) \end{gathered} \quad (9)$$

Prior (Case 2)

$$\begin{gathered} g(j) \sim Bernoulli(\pi_j) \quad j = 1, 2, 3 \\ \pi_j \sim U(0,1) \\ \alpha \sim N(0, \tau_1), \gamma \sim N(0, \tau_2), \eta \sim N(0, \tau_3) \\ \tau, \tau_1, \tau_2, \tau_3 \sim gamma(0.001, 0.001) \end{gathered} \quad (10)$$

Note that this variant is more efficient since it allows simultaneously estimating the weights of all the possible models and parameters.

3. APPLICATION TO THE DATA

The research was conducted in La Lisa municipality, Havana City. In this study were included all reported cases during 2006 and 2007 dengue outbreaks in this municipality. We will show the methodology assuming the 3P logistic model. Table 2 shows the AIC and BIC information criteria for the eight models, as well as the a posteriori weights or probabilities. In addition, in Table 2 is the deviation information criterion and a posteriori probabilities when the models are fitted using the hierarchical Bayesian model and applying the model average with this criterion. Note how the estimates for each information criteria are dominated by the M_2 model, i.e. when $\beta_2 = 0$, so the estimates of the parameter will be very similar to those obtained by this model.

Table 2: AIC, BIC and DIC for model selection and estimated posterior model probabilities using AIC, BIC and DIC approximation.

Models (M_k)	AIC	BIC	DIC	$p_k(AIC)$	$p_k(BIC)$	$p_k(DIC)$
M_1	256.9	268.3	257.6	0.3473	0.1893	0.3224
M_2	255.8	265.7	256.3	0.6019	0.6947	0.6225

M_3	263.3	273.1	263.7	0.0142	0.0172	0.0153
M_4	261.4	269.6	261.8	0.0366	0.0988	0.0399
M_5	336.1	345.9	352.2	2.2E-18	2.7E-18	9.6E-22
M_6	400.5	408.7	401.0	2.3E-32	6.2E-32	2.4E-32
M_7	458.4	466.6	462.5	6.1E-45	1.7E-44	1.0E-45
M_8	468.9	475.5	472.3	3.2E-47	1.9E-46	7.8E-48

Table 3 shows the parameter estimates for this variant when the Akaike weights (AIC) are used. Note how the coefficient β_2 is not significant indicating that if this model is used for inference, the growth rate and therefore the transmission would be the same in both outbreaks. The plot in Figure 1 gives an assessment of the adequacy of this model.

Table 3: Parameter estimates and 95% confidence interval using model-averaging variant with Akaike weight.

Parameters	**Estimate (95% CI)**	**Sig ($Pr > \|t\|$)**
α_{06}	493.49 (487.17,499.81)	$< .0001$
α_{07}	186.07 (178.63,193.52)	$< .0001$
η_{06}	9.3067(9.1963,9.4171)	$< .0001$
η_{07}	9.8263 (9.4869,10.1657)	$< .0001$
R_{06}	4.1056 (3.8427,4.3685)	$< .0001$
R_{07}	3.7517 (3.1183,4.3851)	$< .0001$
β_1	-307.42 (-317.18,-297.65)	$< .0001$
β_2	-0.0332 (-0.0997,0.0333)	0.3186
β_3	0.5196 (0.1627,0.8765)	0.0055
$R_{06} - R_{07}$	0.3539 (-0.3319,1.0397)	0.3028

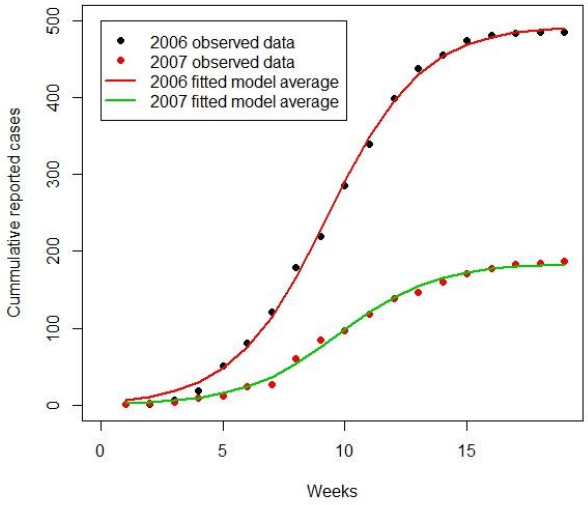

Figure 1. Fitted model averaging using AIC approximation for the 2006 and 2007 dengue outbreaks in La Lisa.

Finally, the results are shown when a Bayesian model averaging is conducted using the Gibbs variable selection. Table 4 shows the posterior probabilities of the models with the posterior distributions according to cases 1 and 2. Note that again, as with AIC, BIC and DIC criteria, the higher posteriori probabilities correspond to the M_2 model, although slightly lower than with the other criteria.

Table 4: Estimated posterior model probabilities with prior using Gibbs variable selection.

Models (M_k)	**Formula for calculating $p_k(GVS)$**	$p_k(GVS)(Case\ 1)$	$p_k(GVS)(Case\ 2)$
M_1	$g(1).g(2).g(3)$	0.1865	0.1592
M_2	$g(1).[1-g(2)].g(3)$	0.5639	0.4822
M_3	$g(1).g(2).[1-g(3)]$	0.062	0.0890
M_4	$g(1).[1-g(2)].[1-g(3)]$	0.1876	0.2696
M_5	$[1-g(1)].g(2).g(3)$	0	0
M_6	$[1-g(1)].[1-g(2)].g(3)$	0	0
M_7	$[1-g(1)].g(2).[1-g(3)]$	0	0
M_8	$[1-g(1)].[1-g(2)].[1-g(3)]$	0	0

Table 5 shows the estimates of the mean of the indicator functions $g(j)$ for cases 1 and 2, in addition to the means of π in case 2 for each j. Observe as for each case, the average of $g(1) = 1$ indicating that the final sizes of the epidemics are significantly different with total certainty.

Table 5: $g(j)$ means using Gibbs variable selection.

$g(j)$	**Mean** (Case 1)	**Mean** (Case 2)	$\bar{\pi}$ (Case 2)
$g(1)$	1	1	0.6657
$g(2)$	0.2475	0.2482	0.4147
$g(3)$	0.7504	0.6414	0.5469

The parameter point estimates and 95% confidence interval in the two outbreaks and for each case using the Gibbs variable selection are shown in Table 6. Note as according to these estimates the parameters β_2 and β_3 are not significant for each case, indicating that there are not significant differences between the turning point and growth rate of both outbreaks.

Table 6: Parameter estimates and 95% credible interval for the Bayesian model averaging using Gibbs variable selection.

Parameters	**Estimate (95% CI) (Case 1)**	**Estimate (95% CI) (Case 2)**
α_{06}	494.6 (487.6,501.9)	494.4 (487.5,501.5)
α_{07}	182.4 (175.3,190.0)	182.6 (175.7,190.0)
η_{06}	9.332 (9.205,9.462)	9.328 (9.207,9.455)
η_{07}	9.474 (4.736,11.35)	9.627 (9.012,10.05)
R_{06}	4.074 (3.807,4.366)	4.077 (3.813,4.365)
R_{07}	4.536 (1.361,12.29)	4.526 (1.343,12.22)
β_1	-312.2 (-322.1,-302.0)	-311.8 (-321.4,-301.9)
β_2	-0.002 (-0.040,0.408)	-0.003 (-0.408,0.405)
β_3	0.142 (-4.639,1.989)	0.299 (-0.341,0.747)

4. CONCLUSIONS

A topic that could be of interest to epidemiologists is the comparison of two single dengue outbreaks based on estimates of key epidemiological parameters: The turning point, the final size and the basic reproductive number R_0. In this study, we used phenomenological models to test hypothesized differences in this this primary epidemiological parameters extending the three parameter logistic and Richards models to a model that take into both dengue outbreaks.

For the comparison of two single dengue outbreaks, three methodological variants are proposed that take into account the model uncertainty using Frequentist and Bayesian approaches. The first variant consists in applying a Frequentist model averaging using AIC and BIC weights. In the second variant, the parameters were estimated using a Bayesian hierarchical model and then applying a model averaging technique using DIC weights. The third variant, completely Bayesian, used simulation technique: Gibbs variables selection. This last approach is more efficient since it allows simultaneously estimating the weights of all the possible models and parameters.

The three methodological variants were shown considering as mean structure the three parameter logistic model. A limitation of considering the Richards model as mean structure is that the number of models to take into account increases considerably thus would be necessary to use more efficient parameter estimate methods. The applicability of the methodologies proposed was shown to the data of two single dengue outbreaks occurred in La Lisa (2006, 2007), Havana, Cuba.
These modeling approaches could be a valuable tool to public health policymakers for comparing single dengue outbreaks in order to evaluate its control measures.

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