Research article

An alternative model to explain the vectorial capacity using as example *Aedes aegypti* case in dengue transmission

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ARTICLE INFO

ABSTRACT

Vectorial capacity (VC), as a concept that describes the potential of a vector to transmit a pathogen, has had historical problems related to lacks in dimensional significance and high error propagation from parameters that take part in the model to output. Hence, values estimated with those equations are not sufficiently reliable to consider in control strategies or vector population study. In this paper, we propose a new VC model consistent at dimensional level, i.e., the definition and the equation of VC have same and consistent units, with a parameter estimation method and mathematical structure that reduces the uncertainty in model output, using as a case of study an *Aedes aegypti* population of the municipality of Bello, Colombia. After a literature review, we selected one VC equation following biological, measurability and dimensional criteria, then we rendered a local and global sensitivity analysis, identifying the mortality rate of mosquitoes as a target component of the equation. Thus, we studied the Weibull and Exponential distributions as probabilistic models that represent the expectation of mosquitoes infective life, intending to include the best distribution in a selected VC structure. The proposed mortality rate estimation method includes a new parameter that represents an increase or decrease in vector mortality, as it may apply. We noticed that its estimation reduces the uncertainty associated with the expectation of mosquitoes' infective life expression, which also reduces the output range and variance in almost a half.

1. Introduction

The VC[1] is a concept that describes vector potential to transmit a pathogen. Garret-Jones in [1] originally described it as "the average number of inoculations with a specified parasite, originating from one case of malaria in unit time, that the population would distribute to a man if all the vector females biting the case became infected" [2]. VC has originally proposed for malaria [3] and, but years later, it was extrapolated for another disease transmitted by vectors as Chagas [4], leishmania [5, 6], dengue [7], and others. Garret-Jones also introduced a mathematical expression to define through Equation (1). We show parameters set in Table 1.

$$VC = \frac{ma^2 p^n}{-\ln(p)} \tag{1}$$

According to [8], Garret-Jones designed and implemented Equation (1) following a series of parameters incorporated in a differential equation system that was proposed by Ross [9] and Macdonald [10], which is considered as the first model that described malaria's dynamic propagation [3, 11]. However, literature states another usual form of representing VC in Equation (2) since the related mortality expression e^{-gn}/g is equivalent to $p^n/\ln(p)$. Both expressions represent the expectation of mosquitoes infective life, the first one in terms of mortality rate and the other one in terms of survival probability (see parameters definition in Table 1) [12, 13, 14].

$$VC = \frac{ma^2 e^{-gn}}{g} \tag{2}$$

The VC equations have followed evolving keeping previous Equation (1) or (2) as basic structures but variating or adding new parameters. Some equations implement an expansion for a multi-strains mosquitoes'

Table 1

VC parameters and its value for Bello municipality. Taken from [25]. Intervals are presented in the form: nominal value ± parameter error ($\bar{x}_i \pm \Delta x_i$).

Parameter	Description	Intervals
m	Mosquito per human proportion	3^{*}
M	Susceptible mosquito population per total mosquito population	0.99^{*}
a	Biting rate	2 ± 2 week^{-1}
b	Mosquito to human probability transmission	0.5 ± 0.5
c	Human to mosquito probability transmission	0.5 ± 0.5
g	Mosquito mortality rate	0.13 ± 0.07 week^{-1}
n	Extrinsic incubation period	0.875 ± 0.375 week
p	Mosquito survival probability	$0.5 \pm 0.5^{**}$

[*] These parameters were fixed and do not report confidence intervals. Thus, they will not be taken in account for posterior analysis.

[**] Theoretical interval for a probability.

populations [2, 15], add delays in different virus developmental parameters [16], include probabilities of mosquito and human infection with the virus [7, 17, 18] or expressions that put VC in function of different mosquito ages in a population [19, 20]. Also, more of these equations have been implemented as a criterion in more efficient control measures, as shown in [20, 21, 22].

However, note that VC is theoretically defined as a daily rate (time^{-1}), but the units of the original Equation (1) are in time^{-2} instead of time^{-1}. This means that the definition and the equation do not have the same consistent units, defined as a dimensional gap pointed out by [12]. Also, for the original equation (1), some biological aspects as the interaction between human-vector and the mortality rate expression have been assumed to be perfect or constant [12, 23]. Hence, we made a literature review and tested the most relevant parameters that take part in the different VC equations of *Ae. aegypti* for dengue virus, to define a new VC basic structure to estimate the potential of a vector to transmit a pathogen, taking as a study case one of the most affected regions in Colombia: Bello (Antioquia). We validated the new VC structure introduced in this paper using Global Sensitivity and Uncertainty Analysis (SA/UA) as a method that allows us to quantify the propagation of uncertainty associated to parameters considered in equation [24].

This paper is distributed as follows: Section 2 describes the first equation selected from literature, parameters analysis, and an uncertainty and sensitivity analysis to propose a new VC basic equation. Section 3 describes the results got in uncertainty analysis, the procedure to change the VC equation and the sensitivity analysis for two VC equations. Finally, we discuss the biological meaning of the new equation, its advantages, and disadvantages.

2. Methodology

2.1. Vectorial capacity equation selected from literature

The VC mainly represents the number of secondaries cases that a mosquito causes in a susceptible human population because of infective interactions per unit of time; Therefore, measuring this rate in the field or lab is impossible. For this, we used mathematical models to estimate the value of the VC. To test a group of biological parameters that take part in VC equations for dengue and malaria, we made a deep search in the literature which covered the last 50 years. For that, we used as keywords *malaria* & *vectorial capacity*, *dengue* & *Aedes aegypti* & *Aedes albopictus* & *vectorial capacity*. We based the search on [2] methodology, using as search engines Google Scholar and Web of Science, in a temporal line that spans from 1960 until 2016. The first criterion to select a paper was that it had to explain or implement any variety of VC equations that described the transmission phenomena for dengue or malaria. We identified that the proposed equations in these papers follow a similar basic structure, where expressions for the mortality rate, the survival probability, the mosquitoes proportion, and biting rate, are common.

After that, we made a theoretical study of the parameters that composed the different VC equations, which had to fulfill the following three criteria: First, the parameters must have a biological meaning according to the disease characteristics in the study site. Second, parameters must be measurable *in vitro* or estimable. Third, the equation must keep the same units proposed in the Garret-Jones definition (time^{-1}) [12]. We see that the units of the CV are bites squared per unit of time. If we understand square bites as infectious interactions, i.e., the process in which an infected mosquito bites a susceptible human which then becomes infected and bitten by a susceptible mosquito that also becomes infected, then it is possible to see that the VC equation talks about the number of secondary infections that the vector produces per unit of time, as Garret-Jones defined.

Finally, we selected as a base model the following Equation (3), that was reported by [7]. Equation (3) describes the expectation of mosquitoes infective life in terms of mortality rate g. Also, it includes two parameters which describe mosquito-human interaction, b and c, and biting rate, a (see Table 1). Equations (1) - (2) originally supposed pathogen perfect transmission, i.e., $b = c = 1$.

$$VC = \frac{ma^2 bce^{-gn}}{g} \tag{3}$$

The parameters that compound VC equations, as a and c, are principally measured in the lab: the experiment to get a comprise putting a female mosquito into a cage where is exposed to human skin and, in a time interval, the number of bites over the human skin is counted [26]. For the parameter c the experiment is to feed the mosquitoes with blood spiked with the dengue virus; then, 7 and 14 days after exposure, the mosquitoes bodies are examined using a cell culture enzyme immunoassay, checking the number of infected versus the total exposed population [27, 28]. The parameter b is mostly estimated using mathematical models as shown in [29, 30]. It is difficult to measure using lab methodologies due to the ethics of tries the probability of a human to become infected after a dengue virus exposure.

2.2. Error propagation (Taylor series)

We implemented a straightforward and fast method for the identification of those critical parameters considered in a VC equation. This method is known as a first order error propagation, as seen in [31, pag. 75]. Given a model $y = f(x_1, x_2 ... x_k)$ and its respective nominal output $\bar{y} = f(\bar{x})$, since $\bar{x} = \bar{x}_1 \bar{x}_2 ... \bar{x}_k$. Where each parameter has its own range, $x_i = \bar{x}_i \pm \Delta x_i$ (see Table 1), we will find analytically error contribution for each of the equation parameters testing the partial derivatives for Equation (4) in $\bar{x}$. Then, we can write model output in the form $\bar{y} \pm \Delta^{(1)}y$ (nominal output ± total error).

$$\Delta^{(1)}y = \left| \frac{\partial f}{\partial x_1} \right|_{\bar{x}} \Delta x_1 + \left| \frac{\partial f}{\partial x_2} \right|_{\bar{x}} \Delta x_2 + ... + \left| \frac{\partial f}{\partial x_k} \right|_{\bar{x}} \Delta x_k \tag{4}$$

For subsequent analysis, we propose the following conventions: PD as the partial derivative term $\left(\left| \frac{\partial f}{\partial x_i} \right| \right)$, PD value as the PD expression tested at the nominal values of parameters ($\bar{x}$), and PE as the absolute value of parameter error, exposed in Table 1 (Δx_i). In that way, the contribution of a parameter x_i to the total model output error can be comprehended as the multiplication of its correspondent PE and PD value.

Observe that a high PD value for a specific parameter suggests a strong correlation between the parameter value and the output range. On the other hand, a large value for the PE of a parameter can lead to a strong correlation, even when its PD value is quite negligible. Noticeably, while the PE of a given parameter is commonly improvable through more accurate measurements, the PD value only depends on the mathematical structure of the model.

2.3. Study site and mosquitoes population

Dengue fever is a viral disease produced by a virus with the same name and transmitted by bites of mosquitoes of *Aedes* gender, where temperature and humidity affect its prevalence [32]. This vector has dispersed in tropical and subtropical zones [33] as the municipality of Bello (Colombia), which is considered as an endemic place with epidemic outbreaks [34]. It has optimal conditions to vector proliferation with a daily average minimum and maximum temperature of 21-22 °C and 27-28 °C during the year, 1300 m.a.s.l. and precipitation of 1300 mm [35].

For Bello and some localities nearby to it, the four serotypes of dengue have been isolated [34]. Because dengue continuously affect these localities, some studies as [25], have focused on the study those mosquito populations dynamics. So we implemented as initial or base parameters those which are estimated for Bello and, in the next section, we proposed a method to estimate population parameters (Mortality rate) from female deaths per day.

2.4. Mosquito mortality rate estimation using statistical distributions

To get an accurate lifetime model, we focused on the expectation of mosquitoes' infective life expression as an uncertainty source inside the VC model. Hence, we fitted the number of females dead per day from mosquito life tables using Weibull and exponential distributions. We built these life tables from immature stages of mosquitoes collected in natural breeding sites in Bello (Colombia) following the procedure in [25].

We reared mosquitoes in the laboratory the two boundary temperatures in Bello 23 ± 1 °C and 27 ± 1 °C, 70 - 80% of relative humidity, with a day length of 12 hours. The eggs of fifth-generation (F5) were submerged in dechlorinated water and the emerged larvae were counted. Afterward, we put emerged adults into 500 cm^3 plastic cages, provided with a 10% sucrose solution and a wet substrate for laying eggs. After six days of post-emerging, females were fed on chicken blood twice per week and we recorded daily adult survivorship. The experimental essays performed for this study were approved by the Comité de Ética para la Experimentación con Animales (CEEA), Colombia.

After getting the number of mosquitoes deaths per day (see supplementary file *MosquitoSupervivence.xlsx*), we fit it to the exponential and Weibull distributions, which are used to describe lifetime modeling [36]. We compared it through linearization of cumulative distribution function (CDF) to define which model fits better to Bello data and gives the best way to estimate the mortality rate and expectation of mosquitoes infective life. Linearization procedure is as follows.

Exponential CDF is given by Equation (5) which is equivalent to $-\ln(1 - F(t)) = tg$, where t defines time, for VC case is equivalent to n. For linearization, we define new variables y, x as $y = -\ln(1 - F(t))$ and $x = t$, then we get the following linear expression $y = xg$. On the other hand, Weibull CDF is given by Equation (6) and, following the previous procedure, we can define new variables y, x as $y = \ln(-\ln[1 - F(t)])$ and $x = \ln t$, then the linear form in this case is given by $y = \eta x + \eta \ln g$. These linear forms allow us to identify the theoretical data distribution, since they should be on a straight line with the linear form of the population distribution $F(t)$, which is replaced by its empirical version showed in Equation (7). Where $I_{\{t_i \le t\}}$ is an indicator function that is one if $\{t_i \le t\}$ and zero in another case.

$$F(t) = 1 - e^{-gt} \tag{5}$$

$$F(t) = 1 - e^{-(gt)^{\eta}} \tag{6}$$

$$\hat{F}(t) = \frac{\sum_{i=1}^{n} I_{\{t_i \le t\}}}{n} \tag{7}$$

Finally, the distribution of the data was also evaluated performing the non-parametric Kolmogorov-Smirnov Goodness of Fit Test (KS), a test used to evaluate the degree of coincidence between the empirical data distribution and specific theoretical distribution (Exponential or Weibull), where the null hypothesis is that the data follow the tested distribution. For these tests, we reject the null hypothesis when the *p*-value is smaller than a significance value of 0.05.

2.5. Global sensitivity and uncertainty analysis

Global Sensitivity and Uncertainty Analysis (GSUA) is the study of how the uncertainty spread from parameters to model output, considering the whole space of the parameters [37]. It is an analysis similar to error propagation analysis (see section 2.2) but it uses a global approach (whole space of parameters) instead of a local one (derivatives for a given point). The global approach has advantages when we try to capture the influence of the full range of parameters or the interaction effects between them [38]; However, it does not allow the interpretation of partial derivatives and parameter errors exposed for error propagation analysis. Hence, we applied error propagation analysis for key parameter detection and global sensitivity and uncertainty analysis for model validation.

We chose variance-based methods for Uncertainty and Sensitivity Analysis (UA/SA) because they are versatile and effective for sensitivity index estimation and uncertainty visualization [37]. Variance-based methods are the computer experiment equivalent of the experimental design for the analysis of the variance of an experimental outcome [39], therefore, these methods require multiple simulations (N simulations) of a model (y) with random parameter combinations in whole parameters space (Monte Carlo simulation). Here y is a VC model with k parameters and their respective uncertainties $y = f(x_1, x_2...x_k)$, $x_i = \bar{x}_i \pm \Delta x_i$ (see Table 1).

From the works of [40] and [37, 38, 41] we can state that variance-based sensitivity analysis try to reach a complete variance decomposition of y in a finite number of terms that depends on parameters and their interactions, and then, it estimates the contribution of each parameter to the model output variance (sensitivity index). We treated Uncertainty Analysis as the visualization of uncertainty propagation from the space of parameters to model output through Monte Carlo simulation [42, pag. 3], and therefore, it is a coupled process with the sensitivity analysis.

The drawback of variance-based methods is their computational cost [38]. Hence, the sensitivity analysis is just used to compute two sets of k indices: the k first-order effects (the contribution of each parameter itself) and the k total-order effects (the contribution of each parameter itself plus all its interactions with other parameters) [37].

Since we want to assess the reduction in model output uncertainty, we compute the k total-order effects (S_{Ti}), estimating Equation (8) as proposed in [37]. Equation (8) must be read as the total sensitivity index for parameter i (S_{Ti}), that is equal to the expected variance that would be left if all factors, except x_i, could be fixed, divided by the total model variance, i.e., the normalized mean-variance with which parameter i contributes to the model output. For a detailed explanation of the Indexes calculation and their interpretation, we refer the reader to [37].

$$S_{Ti} = \frac{E_{\mathbf{X}_{\sim \mathbf{i}}}(V_{x_i}(Y|\mathbf{X}_{\sim \mathbf{i}}))}{V(Y)} \tag{8}$$

Where: $E(\cdot)$ is the Expectation of mean argument, $V(\cdot)$ is the Variance of mean argument, x_i represents the i-th parameter, $\mathbf{X}_{\sim \mathbf{i}}$ represents all the parameters but the i-th one and Y is the model output.

For conclusive UA/SA for VC equations, we applied a variance-based GSUA method proposed by [37] implemented in GSUA toolbox 3.0 [43] for Matlab™2018a. We explored the state-space of k parameters considered for each model through $N = 6000$ samples using a Latin hypercube design. This sample size was chosen to follow Matlab Sensitivity Analysis criteria (to overcome $k * 10$ threshold) and looking for an acceptable computational cost (up to 10 minutes in Intel(R) Core(TM) i7-3770, CPU 3.40 GHz, architecture x64).

Table 2

Error propagation analysis based on Equation (4) for Equation (3) respect to each parameter, we used parameter error (PE) and nominal values shown in Table 1. Partial derivative (PD) corresponds to the term $\left|\frac{\partial f}{\partial x_i}\right|_{\bar{\mathbf{x}}}$, PD×PE corresponds to the term $\left|\frac{\partial f}{\partial x_i}\right|_{\bar{\mathbf{x}}} \Delta x_i$ Relative contribution is each PD×PE value divided by its summation ($\Delta^{(1)}y$). We got values testing correspondent terms in Equation (4) with nominal values of parameters or its PE as showed. Results are shown approach to one decimal number.

Parameters	PD	PD value	PD×PE value	Relative contribution
a	$2abce^{-gn}g^{-1}$	6.9	13.7	43.0%
b	$a^2ce^{-gn}g^{-1}$	13.7	6.9	21.5%
c	$a^2be^{-gn}g^{-1}$	13.7	6.9	21.5%
g	$-a^2bce^{-gn}(n+1)g^{-2}$	58.8	4.1	12.9%
n	$-a^2bce^{-gn}$	0.9	0.3	1.0%
Cumulative		94.0	31.9	99.9%

3. Results

3.1. Mortality rate expression has an important role in vectorial capacity

To determine the key parameters of the VC equation (3), we performed an error propagation analysis using the Taylor series (Table 2). We got a model output value of $VC_1 = 7 \pm 32$ infecting bites per week. Note that there is a high uncertainty for model predictions since the total error for this equation is greater than 400% of the nominal VC value, which suggest that model predictions are not reliable.

According to results in Table 2, mortality rate (g) is the most important parameter for PD value, even so, its PE is the lowest among the equation parameters (see Table 1), and therefore, its relative contribution is not especially relevant regarding to the other ones. Because of the high PE for biting rate (a) and transmission probabilities (b and c), as which can see in Table 1, the relevance of said parameters for Relative contribution in Table 2 is the higher.

We considered a and g as the most important parameters because of the uncertainty of a, based on its PE, and the mathematical importance of g, based on its PD value in Taylor series decomposition. We only chose g as a target to accuracy improvement of Equation (3). We made this decision because the PE of a, as well as b and c, could be improved through measures in lab or field, while a reduction in the PD value of g or n, which are involved in a statistical expression that describes mosquitoes mortality rate, requires a change in the mathematical structure of the VC model.

3.2. Weibull method as better life time model for Aedes aegypti population

Results from the Taylor series (see Section 3.1) show that g is one of the main structural parameters considered into VC; for that reason, it is natural to relate a suitable probabilistic model to explain the mortality rate, using the number of mosquito deaths (see Fig. 1). Usually, the exponential distribution is the lifetime model more used in the literature to describe the expectation of mosquitoes' infective life. However, we used life table information to estimate a Weibull probability distribution that describes the lifetime of the mosquito population in Bello. As can see in Fig. 2 a Weibull model fits better to the lifetime data.

Then, as seen in Fig. 2, the Weibull distribution has a better distribution and linear fit ($R^2 = 0.985$) than the exponential distribution ($R^2 = 0.869$). However, we tested the estimation accuracy for both models by implementing the Kolmogorov-Smirnov test; We got a $p-value$ equal to 0.21 for the Weibull distribution and of $2.2 * 10^{(-16)}$ for the exponential distribution. Since the $p-value$ for the exponential distribution is less than a significance level of 0.01, we reject choosing this distribution.

The parameter estimation for the Weibull distribution expression, $exp(-(gn)^\eta)$, resulted in values of $\eta = 3.44 \pm 0.22$ and $g = 0.175 \pm 0.005$ weeks^{-1}; where η is a new parameter that could be annexed in
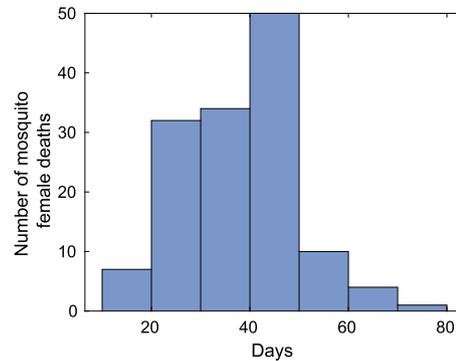
Fig. 1. Frequency of mosquito females death measured in days for population of Bello municipality.

Equation (3). It is a dimensionless parameter that determines if the mortality rate increases or decreases. If $\eta > 1$ then the mortality rate increases, if $\eta < 1$ then decreases. If $\eta = 1$ then we can reduce Weibull expression to an exponential distribution [44]. Also, the new range estimated for g is within the range presented in Table 1; The new range is more reduced but also contained in values reported in lab studies by [25].

3.3. A novel VC equation with a vector-mortality model

After parameter estimation using the Weibull distribution, we changed exponential expression, $exp(-gn)$, with the Weibull expression, $exp(-(gn)^\eta)$; proposing Equation (9) as a general new form for VC. Besides, human and mosquito infection probabilities (b and c) are considered describing vector competence and virus influence [7]. We changed the mosquito per human proportion, m, for a proportion of infected mosquitoes per total mosquito population, M [25]. Finally, note that Equation (9) is a general equation that contains Equation (3) as a specific case. Thereby, it is possible to describe with this new equation a major diversity of vector dynamics.

$$VC = \frac{ma^2bce^{(-gn)^\eta}}{g} \tag{9}$$

3.4. VC equation validation indicates an effective uncertainty reduction

To compare the equation (3) with equation (9), we performed a new error propagation analysis with equation (9) (see Table 3). Compared with values shown in Table 2 we appreciated a reduction into numerical error contribution for all parameters, especially for g, which was reflected in new VC value $VC_2 = 6 \pm 23$. This total error reduction not only depends on the reduction of the PD for g (from 58.8 to 32.8), but reducing the impact of mathematical structure itself (from 94 to 61, PD value column from Tables 2 and 3).

Local methods as the error propagation with Taylor series (previously used in sections 3.1, 3.4) are useful tools for approximations to uncertainty propagation from parameters to outputs. However, global methods lead to a deeper comprehension of parameter relevance and its interactions, taking into account the output space (see Fig. 3). Then, when we used a Weibull distribution to estimate the mortality rate instead of the exponential distribution, we performed a GSUA to test VC output space.

Global analysis indexes, presented in Fig. 4a, keep the ranking got in Taylor series analysis, though contribution percent changed, i.e., there are noticeable interactions between parameters for given ranges. The mortality rate (g) contribution is greater than the estimated with the Taylor series. Fig. 4b shows a significant reduction in contribution percent for parameters associated with the expectation of a mosquito infective life (g, η), hence, VC output uncertainty for Equation (9) depends almost solely on a, b and c, therefore, we reached an improved model for VC.

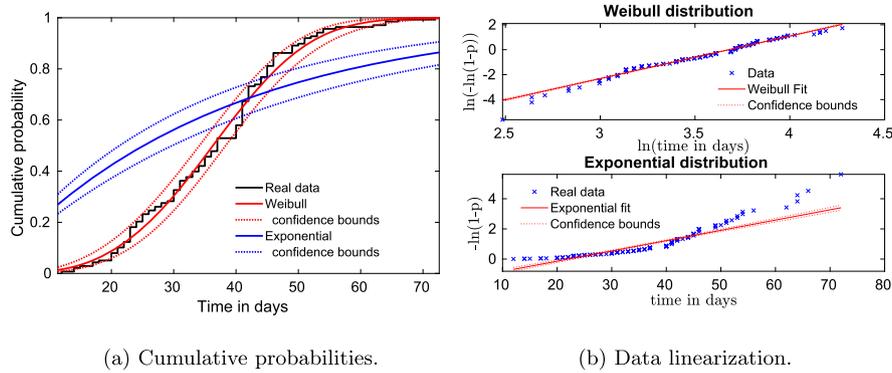(a) Cumulative probabilities.   (b) Data linearization.

Fig. 2. Weibull and exponential distributions fitted to real data using: (a) Theoretical CDF, for those distributions, and Empirical distribution function for real data; (b) linearization of real data using Weibull and exponential probability-probability paper (see section 2.4).
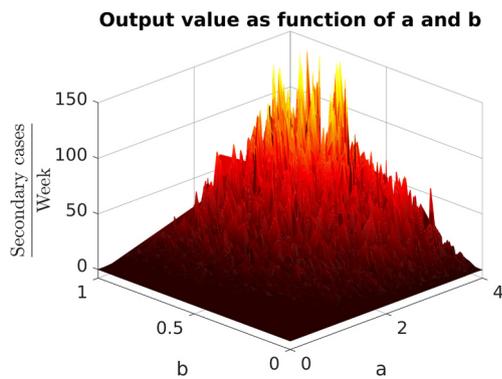

Fig. 3. Mesh graph of VC equation output as a function of a and b based on uncertainty analysis results for Equation (3). The same behavior is evidenced by all paired combinations of a, b, c, and, to a lesser extent, g.

Table 3

Error propagation analysis based on Equation (4) for Equation (9), using parameter error (PE) and nominal values shown in Table 1, except for parameters g and η whose values were introduced in Section 3.2. Partial derivative (PD) corresponds to the term $\left|\frac{\partial f}{\partial x_i}\right|_{\bar{\mathbf{x}}}$, PD×PE corresponds to the term $\left|\frac{\partial f}{\partial x_i}\right|_{\bar{\mathbf{x}}} \Delta x_i$ Relative contribution is each PD×PE value divided by its summation ($\Delta^{(1)} y$). We got values testing correspondent terms in Equation (4) with nominal values of parameters or its PE as shown. We show the results approach to one decimal number.

Parameters	PD	PD value	PD×PE value	Relative contribution
a	$2\,a\,b\,c\,e^{-(g\,n)^{\eta}}\,g^{-1}$	5.7	11.4	49.6%
b	$a^2\,c\,e^{-(g\,n)^{\eta}}\,g^{-1}$	11.4	5.7	24.8%
c	$a^2\,b\,e^{-(g\,n)^{\eta}}\,g^{-1}$	11.4	5.7	24.8%
g	$-\frac{a^2\,b\,c\,e^{-(g\,n)^{\eta}}\,(\eta(g\,n)^{\eta}+1)}{g^2}$	32.8	0.2	0.7%
n	$-a^2\,b\,c\,\eta\,e^{-(g\,n)^{\eta}}\,(g\,n)^{\eta-1}$	0	0	0%
η	$-\frac{a^2\,b\,c\,e^{-(g\,n)^{\eta}}\,\log(g\,n)(g\,n)^{\eta}}{g}$	0	0	0%
Cumulative		61.4	23.0	99.9%

Fig. 5 displays the results for the uncertainty analysis (UA) of equations (3) and (9). We chose the 6000 random parameter combinations for the Monte Carlo simulation, as stated in Section 2.5. Since the output of both of the VC models for every simulation is a scalar (a single number), the UA gave us an output vector for each model. We considered the output space of each model as the range of its output; Further, we quantified each model output uncertainty as the variance of its output vector. As you can see in Fig. 5 (box plot and histogram), vector of outputs for equation (9) are less dispersed, and therefore there is a significant reduction in output space and variance regards to results for equation (3) (from [0-156] to [0-87] and 278 to 123 respectively).

To understand why variance contributions of a, b, c and g are closer for GSUA techniques (Fig. 4a) than in Taylor series decomposition analysis (Table 1), we present output values for Equation (3) as a function of paired combinations for a, b, c and g (Fig. 3). Note that output values do not show preferences regarding one parameter more than the other, i.e., high and low output values are indeed equally related with extreme parameter values.

Summarizing, to reduce the contribution of mortality expression to VC model output uncertainty, we introduce a new model (Equation (9)), a method to estimate the parameter g and a new required parameter η. Then, we assessed the new model looking for a reduction in its output space as well as its uncertainty regarding the model of Equation (3) (Fig. 5). The most remarkable goal reached through Equation (9) is the reduction in output space and variance, which besides resulting in Fig. 4b, shows an accurate estimation of parameters g and η.

4. Discussion

VC has been created to determine mosquitoes' potential to infect. Its mathematical representation has been criticized because of main lacks like: (I) dimensional inconsistencies reported for several equations which implement Equation (1) as a basic structure and (II) assumptions as pathogen perfect transmission ($b = c = 1$) [8, 23] and exponential mortality expression [20, 45], these cause that VC would be mis-estimated. In this paper we avoided the mentioned disadvantages proposing Equation (9) that implements Equation (3) as a basic structure, adding a new parameter η, proposing a method to estimate accurately η and g, and testing b and c in its whole range.

We studied the expression of mortality included in the VC in this article, where we identified g as a relevant parameter within the equation because of its importance at a mathematical level, which influences the final value of the VC. Therefore, as we reduce the uncertainty related to the expectation of mosquitoes' infective life, then VC values depend only on the remaining VC parameters (a, b, and c). Hence, the researcher must measure either parameter meticulously or, in other cases, estimated using systems of differential equations, if it is difficult to measure *in vitro* and *in vivo*. In the Bello's case, we obtained a very large VC output interval, principally because of uncertainty in a, b and c, bringing about a VC value that is not informative for this population.

Because of the high value of the VC error, it is necessary to find different ways to shrink the intervals of parameters used to estimate it. We focused on the mortality rate and estimated it through statistical distributions such as exponential and Weibull, which have been used to describe lifetime models [36]. By making estimations using Weibull distribution, we got accurate intervals and a more robust mathematical expression; Therefore, with this method, we diminished the uncertainty related to the expectation of mosquitoes infective life.

We identified that the mortality expression classically described as exponential in the literature was not adequate to describe mortality

(a) Selected Equation (3)

(b) Proposed Equation (9)
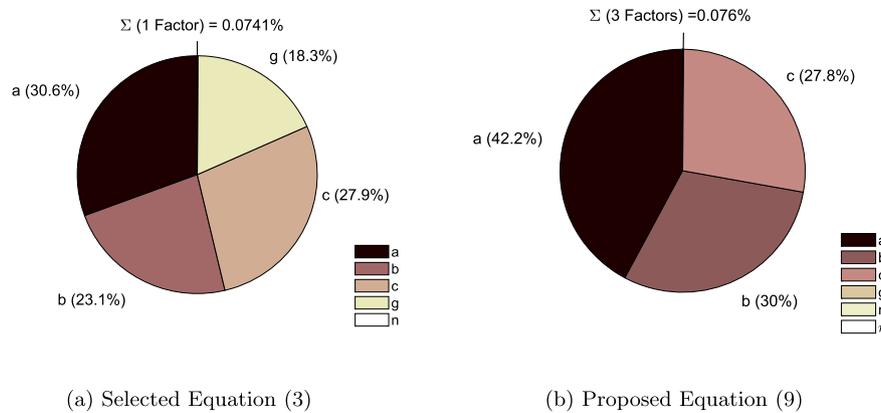
Fig. 4. Total Sensitivity indexes (S_{T_i}) for both of the equations. Percent values represent the contribution to total output variance. When an index is almost zero means that does not matter the value assigned to the parameter within a specified range, the output value should not be significantly affected, therefore, either the parameter is well estimated or is irrelevant within the model.
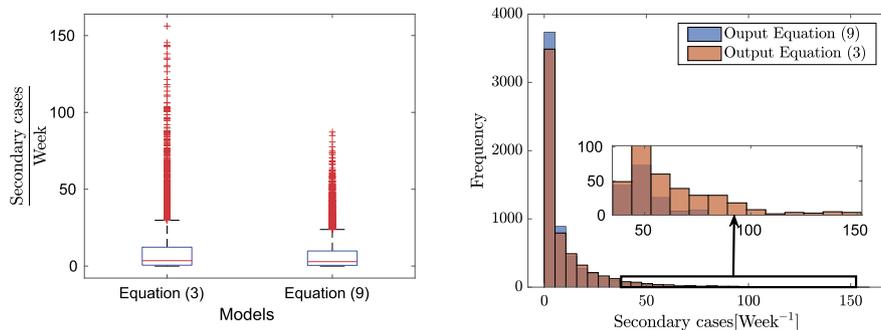
Fig. 5. Uncertainty analysis for selected Equation (3) and proposed Equation (9) with 6000 random parameter combinations. Extreme value for the proposed equation concerning selected one shows a significant reduction in output range (from 156 to 87), further, output values are less dispersed (from a variance of 278.4 to 122.6) for proposed one, which is understood as uncertainty reduction.

phenomena in the mosquito population in Bello. Here, we showed that the expectation of mosquitoes' infective life in Bello follows the Weibull distribution instead of the exponential distribution. Hence, we added the parameter η to the VC equation.

We did not find, in the literature review, a Weibull distribution proposed as mosquitoes mortality expression for VC. Nonetheless, this distribution has been implemented to describe longevity in growth and food variability of *Ae. aegyptis* [46], larval and adult survivorship at temperature variance in *Anopheles gambiae* [47] or senescence in insect populations [48].

When we implemented Equation (9) with new parameters associated with the expectation of mosquitoes infective life from Weibull distribution, we noticed that this change helped to reduce the output space and variance by almost 50%. Thus, it is important to make a preliminary study to choose the distribution that best explains the behavior of the biological system of interest. Since not all species or populations of vectors follow the same distribution and, therefore choose a less-indicated distribution can generate inconsistent values in the VC estimation, misestimating it.

Different authors separated parameters as *b* and *c* [16, 49]. However, since said parameters are exposed as consecutive multiplications and have the same range ([0,1]), then they share the same behavior and its value is close to being equally relevant according to the perspective of systems identification theory [50, ch. 19]. Parameters *b* and *c* must be unidentifiable ones, e.g., even when we know that they have the same S_{T_i} value, it is not feasible to estimate it (see indexes for *a* and *b* in Fig. 4). Thus, because of UA/SA results, we should represent those parameters as a single term of disease transmission, as other authors have proposed [18].

The global UA/SA of Equation (3) conserved the relevance ranking got from Taylor series analysis. Remarkably, the relative contribution of each parameter suffered notable changes, e.g., parameter *a* dropped from 43.0% of error contribution for Taylor series to 30.6% for the global method. Mentioned changes could be explained by appealing to noticeable interactions between parameters. Those interactions were registered because of the applied global method and can be intuitively visualized in UA results (Fig. 3). As seen, combinations leading to extreme output values correspond to parameter values close to the upper and lower ends for the intervals of *a*, *b*, *c* and *g*. The sensitivity analysis shows that *a* contributes mainly to the error in the estimated value of VC from Equations (3) and (9). Because of *a* is a rate and *b*, *c* are probabilities (hardly measurable), we suggest for future studies to measure *a* as carefully as possible in the lab to reduce its confidence interval and therefore the final VC uncertainty. Thus, with the proposed method to estimate *g* and η, a better VC approximation will almost depend on an accurate estimation of *a*.

Because of the mortality analysis combined with the results of the sensitivity analysis, we suggest Equation (9) as an adequate basic structure to describe the VC phenomenon in the municipality of Bello. Also, note that the equations that implement the exponential expression of mortality and probabilities of infection are special cases of the Equation (9) in which the value of η is equal to 1. We can implement the proposed equation in more cases than the classical exponential-based equations. For future investigations, we propose to select different locations and carefully estimate VC parameters to compare both Equations (3)-(9) and determine the best fit for VC. Thus, it will only be possible by reducing the uncertainty in the VC parameters.

5. Conclusion

From the literature analysis of VC equations, it was possible to propose a basic structure that reduces VC output space. We attested that the most important parameters in VC vary according to its confidence intervals and the mathematical structure itself. Also, during the review of biological concepts that compose VC, it was possible to conclude that the mosquito mortality expression depends on the biological characteristics of the mosquitoes population. For the specific case of Bello municipality, we proposed an Equation that includes *a*, *b*, *c* parameters and a mosquito mortality expression based on Weibull distribution (Equation (9)), which is a general equation that includes the classical VC formulation as a special case. Finally, we verified through uncertainty and sensitivity analysis that it is possible to estimate a most accurate VC value implementing characteristic population parameters and using tools like statistical analysis.

Declarations

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