FACULTAD DE POSGRADOS

THE DYNAMICS OF CUTANEOUS LEISHMANIASIS IN THE PRESENCE OF BIRD RESERVOIRS AS A TOOL FOR DISEASE SURVEILLANCE IN ECUADOR

Trabajo de Titulación presentado en conformidad con los requisitos establecidos para optar por el título de Magister en Ciencias Biomédicas

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DECLARACIÓN PROFESOR GUÍA

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DECLARACIÓN DE AUTORÍA DEL ESTUDIANTE

“This thesis is the original work of its author, who has worked in conjunction with a team of researchers. A version of this work is being prepared for publication in the professional scientific literature with the following co-authors: Marlio Paredes, Emmanuel J. Morales-Butler, Mayteé Cruz-Aponte, Leon Arriola, Varsovia Cevallos, Patricio Ponce, Anuj Mubayi”.

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RESUMEN

La malaria es una enfermedad infecciosa producida por parásitos protozoarios del género *Plasmodium* y transmitida por mosquitos hembra del género *Anopheles*. Alrededor de 3.3 mil millones de personas en el mundo entero corren el riesgo de contraer la enfermedad. En el 2015 en Ecuador los casos ascendieron a 558. Existen alrededor de 465 especies de *Anopheles* reconocidas en el mundo. El conocimiento de la diversidad de especies de *Anopheles* en cada país es indispensable con el fin de comprender la dinámica de los vectores y de la enfermedad. La región ITS2 de ADN ribosomal es un marcador molecular, tiene regiones conservadas para el diseño de cebadores universales que permiten la amplificación de la región y a la vez posee suficientes sitios variables, aptos para diferenciar especies estrechamente relacionadas. Para la identificación se utilizó la técnica de PCR convencional. Se analizaron 57 secuencias para la elaboración del árbol filogenético. *An. trinkae* fue la especie de mayor abundancia con el 31,6% del total, seguido del complejo cruzii con 29,8%, *An. albimanus* con el 28,1%, *An. rangeli* con el 5,3%, *An. pseudopunctipennis* 3,5% y *An. apicimacula* con el 1,7%. Todas las especies identificadas, a excepción de *An. apicimacula,* han sido reportadas como vectores de malaria en otros países.

ABSTRACT

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium* and transmitted by female *Anopheles* mosquitoes. Around 3.3 billion of people in all the world have the risk of contracting the disease. In 2015 Ecuador had 558 cases of malaria. About 465 *Anopheles* species are recognized in the world. Knowledge of the diversity of *Anopheles* species in each country is essential in order to understand the dynamics of the vector and the diseases. The ITS2 region is a ribosomal DNA molecular marker, it has conserved regions for the design of universal primers that allows the amplification of the region and simultaneously has variable sites, apt to differentiate closely related species. Conventional PCR technique was used for identification. 57 sequences were analysed for the development of the phylogenetic tree. *An. trinkae* was the most abundant specie with 31.6% of the total, followed by the cruzii complex with 29.8%, *An. albimanus* with 28.1%, *An. rangeli* 5.3%, *An. pseudopunctipennis* 3.5% and *An. apicimacula* with 1.7%. All the species identified except *An. apicimacula* have been reported as malaria vectors in other countries.

INTRODUCTION

Leishmaniasis is a disease caused by a protozoan that is transmitted by sand flies of the subfamily Phlebotominae of the genera *Lutzomyia, Nyssomyia, Migonemyia, Bichromomyia, Pintomyia, Trichophoromyia* (Andressa, 2014) in the Americas. The female sand flies are infected when they bite a natural reservoir (such as birds) or humans with Leishmaniasis and transmit the Leishmania parasite (Kato et al., 2008). Ecuador is a country located in north-west of South America that is extremely ecologically diverse. Ecuador's ecology ranges from dry forest in the coast, cloudy forest in the Andes to tropical rain forest in the Amazon lowlands (Calvopina, Armijos, & Hashiguchi, 2004).

The first case of Leishmaniasis in Ecuador was reported in 1920 (Cadena, 1999). Clinical diagnosis is the only method to confirm cases and to get officially reported. CL is a public health problem in Ecuador because of its wide distribution, mainly in rural areas of the coast, highlands and eastern lowlands. Leishmaniasis is present in 23 out of the 24 provinces of the country, except in the Galapagos Islands ("WORLD HEALTH ORGANIZATION," 2016). Limited studies have been conducted to determine possible reservoirs of CL, these studies have identified three mammalian species with the parasite including the sloth *Choloepus hoffmanni didactylus*, the squirrel *Sciurus granatensis*, and the kinkajou *Potos flavus* (Hashiguchi & Gómez Landires, 1991). Serological studies in the Pacific and Andean region, determined the infection in dogs with the same human strain isolated in the respective regions, but nevertheless the study does not distinguish whether dogs are incidental or reservoir hosts and seem to be a victim-host as humans are (Calvopina et al., 2004). Studies in Brazil indicated, as a potential risk factor for visceral leishmaniasis, the proximity of humans chicken breeding setups, although transmission via chickens has not been well explained (Otranto et al., 2010).

New molecular techniques allowed estimation of the biting rate of vectors on various hosts, which makes possible to determine the preferences that influence transmission of the parasite (Simpson et al., 2012)In Ecuador, birds were determined as the main blood meal source of sand flies using molecular

analysis at a leishmaniasis hyper endemic area in the coastal region (Anaguano, Ponce, Baldeón, Santander, & Cevallos, 2015b). Since re-emergent infectious disease outbreaks are increasing, it is of interest to gain understanding of the dynamics of the diseases.

The development of mathematical models for infectious diseases, is determined by their biological assumptions, which influence the predictive potential of the model (Anaguano et al., 2015b). The development of mathematical models for infectious diseases, determined by their biological assumptions, which influence the predictive potential of the model (Wonham, Lewis, Rencławowicz, & Van Den Driessche, 2006). Mathematical models can be used to design control strategies, taking as a reference the decrease of the basic reproduction number R_0 which is the average number of secondary cases of infection as a result of the introduction of a primary infection into a completely susceptible population. Finding this number allows one to set the threshold of a disease outbreak (Luis Fernando Chaves, 2008).

There has been limited studies for understanding the transmission dynamics of Cutaneous Leishmaniasis (CL) via mathematical models. Chaves *et al*., (Luis Fernando Chaves, Cohen, Pascual, & Wilson, 2008) suggest models to describe the dynamics of infection among vectors, humans and consider dogs and donkeys as reservoirs of the parasite. The same author (Luis Fernando Chaves, 2008) analyzed the relations in the changes produced by humans and deforestation, and suggested that deforestation increases the risk factors for infection by CL by a certain level. A simple mathematical framework was designed to illustrate limitations in the ecological knowledge of the transmission of Leishmania that are required to understand the life cycle of the parasite (Luis F. Chaves, Hernandez, Dobson, & Pascual, 2007). Other study on the transmission of CL using models considered incidental hosts for the parasite and reservoir (Luis Fernando Chaves & Hernandez, 2004). The dynamics of the infection in two hosts and a single vector, in two endemic localities for CL were analyzed and the differences in the value of R_0 were determined (Rosales & Yang, 2007).

The manual of procedures for disease control of the Ecuadorian Ministry of Public Health (MSP in Spanish) recommends determining possible foci of the disease once a case of leishmaniasis has been reported from the region, spraying of dwellings of infected patients and identifying possible reservoirs and its management (Ministerio de Salud Pública del Ecuador, 2013). The current aim of MSP-Ecuador includes understanding the impact of ongoing interventions in the face of limited surveillance and quantifying sand fly biting rates among various hosts. The goal of this study is to extend the ongoing government efforts in understanding complex cycles of Leishmaniasis and estimating its true burden. Specifically, the study (i) quantifies infection rates in birds and humans, (ii) explains role of reservoirs birds on the transmission dynamics of CL, (iii) estimates case underreporting levels, and (iv) suggests effective control policies.

A mathematical model is developed and analyzed to capture the dynamics of CL infections in the presence of bird reservoirs and limited reporting of cases, as well as incorporate mechanisms of parasite infection in sand flies and humans, using data from vector trap sampling and reported cases. This study is expected to assist in design of an early warning system for health authorities and to take specific actions on vector control and reservoir interventions as a response to Leishmaniasis outbreaks.

METHODS

Monitoring of sand flies was conducted in Valle Hermoso, Santo Domingo de Los Tsachilas, Ecuador. Phlebotominos were collected during the dry season, in July 2013 and during the rainy season, in March 2014. The samples were captured with the Centers for Disease Control and Prevention (CDC) miniature light traps. The traps were placed in six transects, 150 meters apart. Specimens collected were killed and stored at -20ºC and transported to the laboratory. Specimens were identified, counted and classified into three groups: blood fed, unfed and gravid females. Females with blood meals were easily recognized by the presence of engorged abdomens. Females abdomens were dissected for DNA analyses. DNA was extracted, amplified and sequenced to identify the potential food source and identify parasitic infection in each sand fly (Anaguano et al., 2015b). Epidemiological data of the Province were obtained from 2009 to 2011, from the Ministry of Public Health.

The reported cases of Leishmaniasis in Ecuador represent an underestimation of the true burden, like in other countries of the region. Since, the cutaneous and mucocutaneous leishmaniasis are non fatal diseases, the population from rural and distant areas are not diagnosed.

The Leishmaniasis cases were obtained directly from the patients who attend the health units for treatment. The epidemiological surveillance of leishmaniasis cases is collected by the Surveillance, Epidemiology Unit of the Ministry of Health (MSP) and the reports are accessible through the technological data platform, Sistema Integrado de Vigilancia Epidemiológica (SIVE in Spanish). According to MSP, 1,002 cases have been reported in 2015. Pichincha, Esmeraldas and Santo Domingo provinces contributed.

The unavailability of historical data can be attributed to many factors, including the lack of notification. The reasons for the underreporting include lack of resources (both personnel and equipment), the tendency to report only the most serious cases and lack of information from private health centers among others (Chan, Sahai, Conrad, & Brownstein, 2011). In Panama, the underreporting of

cutaneous leishmaniasis is attributed to the lack of diagnostic methods and the need to improve access to health services (Dutari & Loaiza, 2014).

Projections based on literature of each region were used to establish probable degrees of underreporting for these countries. According to this study, Ecuador reported 1,724 incidence cases of CL between 2004 and 2008 and the incidence yearly estimated were between 4,800 and 7,900 cases (Leishmaniasis Worldwide and Global Estimates of its Incidence (Alvar et al., 2012).

Model Description

A compartmental epidemiological modeling framework is proposed to model zoonotic parasite transmission in a community of two hosts with a single vector (See Fig. 1). The model considers parasite transmission between the vector, and two categories of hosts: a preferred by the vector (birds) and the human population like an alternative host.

Our model adds an additional compartment that corresponds to the reported cases, considering that in rural areas there is no access to conventional treatment, traditional and ancestral knowledge methods are used (Calvopina et al., 2004).

The human host is divided into classes of susceptible (S_{h1}), infected (I_{h1}), infected reported (P_{h1}) and recovered (R_{h1}) individuals. The size of the total populations is $N_{h1}=S_{h1}+I_{h1}+P_{h1}+R_{h1}$. Both vector and birds hosts are divided into classes of susceptible (S) and infected (I) individuals so the total population size is N = S + I. The variables for the vector are indicated with subscript *v* and birds with subscript *h2*.

Assumptions

The model of the Cutaneous Leishmaniasis transmission dynamics is divided into three groups: Humans, Vector and Birds. Some assumptions are required in each group for the construction of the model.

Human population

The sand flies bite humans at a constant rate (*b*). People recover from the infected population to become susceptible again. Not all the people are reporting the disease. Infected people do not die due to the disease. Population remains constant. Reported infected individuals receive effective treatment and recover faster than unreported infected individuals that are assumed to be non-infectious.

Vector population

Sand flies bite humans and birds at different rates. They can infect humans and birds. The birth and death rates as a result are equal. Sand flies can get infected from humans and birds. Sand flies do not die due to the disease. Population remains constant.

Birds population

Sand flies bite birds at a constant rate (*b*). Birds can get infected due to bites from infected sand flies. Infected birds can transmit the infection to sand flies and there is no disease induced deaths in infected birds. Bird population remains constant.

Method of Model Fitting and Estimation of Parameters

Estimates of highly uncertainty model parameters such as the probability of successful transmission of infection from vector to human host given a bite, β_1, the probability of effective transmission from human host to a vector given a bite, β_2, and the reporting rate, γ_2 are identifiable from data by fitting the vector-host epidemic model to the 2011 Cutaneous Leishmaniasis cumulative incidence data via the weighted least squares procedure (see Appendix).

Parameter Sensitivity Analysis on Relevant Model Quantities

Sensitivity analysis (SA)(L. Arriola & Hyman, 2009; L. M. Arriola & Hyman, 2007) is used to quantify the effects of uncertainty of a model's input parameters δp, and the subsequent uncertainty of the model's output δu.

When the model uses parameter estimation, SA is needed:

- When the observational data u, which is used in estimating parameter values p,
  has significant uncertainty,
- When there are unknown or unspecified parameters p that must be estimated,
- In order to quantify the inevitable effects of parameter uncertainty δp on the uncertainty in the model predictions δu.

SA provides several useful results:

- Allows for prioritization of the most influential parameters on the model output, to the least important parameters,
- Quantifies those intervention strategies that the modeler can affect.

Mathematical analysis

Clearly, the disease free equilibrium point of our model is

$E_0 = (N_{h1},0,0,0,N_v,0,N_{h2},0)$ (1)

We use it to calculate the basic reproduction number of the model which is given by

Sand Fly-Human Interaction | Human-Sand Fly Interaction

$$R_0^2 = \left(\frac{b\beta_1}{u_v}\right)\left(\frac{N_{h1}}{u_v N_{h1} + N_{h1}}\right)\left(\frac{b\beta_2}{\gamma_1 + \gamma_2 + \mu_{h1}}\right)\left(\frac{N_v}{\alpha_v N_{h2} + N_{h1}}\right) + \left(\frac{b\widetilde{\beta_1}\alpha_v}{u_v}\right)\left(\frac{N_{h2}}{u_v N_{h2} + N_{h1}}\right)\left(\frac{b\beta_2\alpha_v}{u_{h2}}\right)\left(\frac{N_v}{\alpha_v N_{h2} + N_{h1}}\right)$$

Sand Fly-Birds Interaction | Birds-Sand Fly Interaction

Remark :1 Note that R_0 depends on human intervention, reservoir management, and vector control related parameters.

In the Appendix we have included a mathematical proof of the existence of an endemic equilibrium point.

Remark 2: The analysis suggest that if $R_0>1$ the CL will become endemic whereas if $R_0<1$, CL can be controlled.

RESULTS

In order to analyze the behavior of the model, we simulate various scenarios of leishmaniasis infection. The parameter estimates used in these simulations can be seen in Table 1 of parameters.

Parameter Estimation

Populations: It is assumed that all the populations are constant, human, vectors and birds. According to the National Institute of Statistics and Census, INEC (for its acronym in Spanish), the town of Valle Hermoso had 10,000 inhabitants in the year 2010, date of the last survey registered.

Feeding for Preferred Host (α_v):

A study was conducted in Valle Hermoso, Santo Domingo de Los Tsachilas province, Ecuador, to determine the source of blood for phlebotomine sand flies. Valle Hermoso is a hyper-endemic area for leishmaniasis. A total of 442 female sandflies were collected and classified as non-engorged and engorged. The 106 engorged females were identified morphological and selected for blood meal identification by PCR technique.

84 individuals of these were positive for blood birds.

$$\alpha_v = \frac{sand\ flies\ with\ blood\ birds}{females\ sand\ flies\ engorged}$$

We estimated the proportion of blood meal sand flies as 0.7924.

Probability Human Host Transmission to Vector (β_1):

In such study were found that the 106 samples of engorged females, 42 was positive for the leishmaniasis and 22 were positive for blood of mammals, by what we estimate the likelihood that a sand fly is infected by the bite to a human is 0.08223.

$$\beta_1 = \frac{sand\ flies\ with\ blood\ mammals}{females\ sand\ flies\ engorged} * \frac{infected\ sand\ flies}{females\ sand\ flies\ engorged}$$

Probability Birds Transmission to Vector($\widetilde{\beta_1}$):

In the same study were found that the 106 samples of engorged females, 84 was positive for blood birds and 42 were positive for the leishmaniasis; by what we estimate the likelihood that a sand fly is infected by the bite to bird is 0.3139.

$$\widetilde{\beta_1} = \frac{sand\ flies\ with\ blood\ birds}{females\ sand\ flies\ engorged}$$

Probability of effective transmission of parasite (β_2):

The transmission between infectious human or bird (reservoirs) and sand fly, when this bite them, was assumed to be 0.25 according to literature.

Per capita rate immunity lost (δ):

In Peru was carried a prospective longitudinal survey of CL. Clinical and demographic data were collected and the results indicated that the recovery rate is 0.0033 per day.

Sand fly death rate (μ_v):

In the same study, the death rate of sand flies is estimated to be 1/14 day^{-1}. We assumed this amount for our calculations.

Biting rate (b):

The per capita biting rate of sand flies b is equal to the number of bites received per human from sand fly due to conservation of bites mechanism.

Infection period (γ_1), (γ_2):

The CL is distinguished by the presence of lesions which then ulcerate; lesions may be multiple, rounded and sometimes without pain. It may appear 15 days after the bite of an infected vector (γ_2). Sometimes these patients are cured spontaneously in an average period of 15 months (γ_1)

Infection period (σ):

In the treatment pentavalent antimony derivatives as meglumine antimoniate and antimony sodium stibogluconate are used. These drugs are recommended

by WHO. Treatment may be repeated 3 times at intervals of 15 days. The dose applied to children and adults, with reference to body weight.

Estimates of highly uncertainty model parameters such as the probability of successful transmission of infection from vector to human host given a bite, $\beta_{1,}$the probability of effective transmission from human host to a vector given a bite, $\beta_{2,}$ and the reporting rate, (γ_2) are identifiable from data by fitting the vector-host epidemic model to the 2011 Cutaneous Leishmaniasis cumulative incidence data via the weighted least squares (WLS) procedure (see Appendix).

Curve Fitting and Estimation Using Least Square Method

Vector density is critical to the establishment of the Leishmaniasis in susceptible regions. Using field surveillance data, intensity of transmission (via feeding preference) through reservoirs hosts (birds) increases estimates of $\boldsymbol{R_0}$. Improvement in surveillance linearly decreases prevalence in human hosts.

$\boldsymbol{R_0}$ distribution: The distribution of $\boldsymbol{R_0}$ from uncertainty quantification via fitting procedure. The distribution is computed using 1,000 simulations. The estimated $\boldsymbol{R_0}$ value is 3.9.

Sensitivity analysis of R_0

A global sensitivity analysis was performed to identify the parameters with the greatest influence on the model to optimize the structure of the model.

In this analysis we use a standard measure of global sensitivity:

the method of partial rank correlation coefficient (PRCC) (Saltelli, Ratto, Tarantola, & Campolongo, 2006). It is well known that PRCC performs well provided the model outputs varies monotonically with respect to each input variable (model parameter). A partial rank correlation coefficient (PRCC) was obtained for 13 parameters used in the Leishmaniasis model with respect to $\boldsymbol{R_0}$.

The sensitivity analysis (SA) shows that model parameters such as human mortality (μ_{h1}), infectious period (γ_1), infectious period before reporting (γ_2), birds mortality (μ_{h2}), and sand flies mortality (μ_v) statistically have a significant influence on the prediction of $\boldsymbol{R_0}$ with a negative correlation. Model parameters

such as parameter 1 (μ_{h1}), parameter 2 (σ), parameter 3 (δ), parameter 4 (μ_{h1}), and parameter 5 (γ_1) are statistically irrelevant on the prediction of $\boldsymbol{R_0}$. Lastly, parameters such as parameter 7 (b), parameter 8 (β_1), parameter 9 (α_v), parameter 10 ($\widetilde{\beta_1}$), parameter 12 (β_2), statistically have a significant influence on the prediction of $\boldsymbol{R_0}$ with a positive correlation. Sand fly related parameters are most influential on the prediction of $\boldsymbol{R_0}$, followed by parameters for reservoir hosts and parameters related to humans. These results strongly support the need to improve the monitoring of the sand flies, as well as the reservoir (bird) population. In other words, this SA provides a specific intervention /monitoring strategy for controlling Leishmaniasis in endemic areas in Ecuador.

We observe the contributions of each of the model parameters. The analysis showed that five parameters with high negative index; four with near 0 index and five with positive index. There is a strong negative correlation between μ_v and $\boldsymbol{R_0}$ and a strong positive correlation between β_1 and $\widetilde{\beta_1}$ with $\boldsymbol{R_0}$ (See Figure 2).

Sensitivity analysis on $\boldsymbol{R_0}$ confirms the need to improve the monitoring of the sand flies and the reservoirs (birds) population.

The analytical computation supports our numerical global sensitivity results. Sand fly related parameters are most sensitive to $\boldsymbol{R_0}$, followed by parameters for reservoir hosts and parameters related to humans.

The analytic expressions for the SI's of $\boldsymbol{R_0}$, with respect to the relevant parameters are given in Appendix. In Table 2, we give numerical estimates in decreasing order of importance.

In other words, a 1% increase in α_v yields approx 0.93% increase in $\boldsymbol{R_0}$ whereas a 1% increase in N_{h1} yields approx 0.93% decrease in $\boldsymbol{R_0}$, with similar estimates for the sensitivity with respect to the other parameters.

DISCUSSION

A mathematical model can be defined as the set of equations that help to understand and describe the dynamics of infection between vectors and hosts (Luis Fernando Chaves, 2008), the model presented in this paper describes the interactions between the vector responsible for the transmission of Cutaneous Leishmaniasis, and its two main hosts, humans and birds.

Brazil lead the effort in conducting studies on food preference in sandflies, their results suggest that *Lutzomyia longipalpis* (the vector for transmission of visceral leishmaniasis) has a preference for birds (Afonso, Duarte, Miranda, Caranha, & Rangel, 2012). On the other hand, a study carried out in a costal town in Ecuador shows that birds are the preferred blood source for several species of phlebotomus (Anaguano et al., 2015b). At the same time, Anaguano's work serve as evidence that there are differences in the abundance of sand flies species and therefore food preference during the dry and wet season, which would be consistent with the epidemiological data reported by the Ministry of Health.

In the simulations it can be observed that there is a wide gap between the reported (P_{h1}) and the infected cases (I_{h1}), confirming our hypothesis that there are an under reporting of the disease.

Under reporting is a result of difficult access to endemic areas, registration system failures and patients diagnosed and treated in private medical centers (De Lima, Borges, Escobar, & Convit, 2010).

The simulations under initial conditions and using parameters reported in literature, show the existence of a peak around the 50th week, coinciding with the outbreak reported by the epidemiological time series data. These results suggest that the system can be adjusted if the field data increase.

On the other hand, we can observe a direct proportional correlation between increase of feeding for preferred host or the time to reporting a case with decrease the infected human population. The relationship between the increase

of α_v (feeding preference) and the decrease on infected humans shows the human influence on the ecological changes such as deforestation.

The sensitivity analysis showed that vectors are very important in epidemic development, and the leishmania transmission by birds will increase $\boldsymbol{R_0}$. The next steps will be the analysis of all the parameters and use field data to validate the model. Sensitive analysis confirms the necessity of improving the monitoring of the sand flies and the bird population.

The simulations performed with the variability of the populations of birds, show that these hosts have a very important role in the dynamics of the transmission of the disease, so increase the data about infection in birds is a very important point to validate the model. This work aims to provide a tool for decision-making in the control of leishmaniasis in endemic areas of Ecuador.

Vector density is critical to the establishment of the Leishmaniasis in susceptible regions. Using field surveillance data, intensity of transmission (via feeding preference) through reservoirs hosts (birds) increases estimates of $\boldsymbol{R_0}$. Improvement in surveillance linearly decreases prevalence in human hosts. Sensitivity analysis on $\boldsymbol{R_0}$ confirms the need to improve the monitoring of the sand flies and the reservoirs (birds) population. This study provides a tool for decision-making in the control of Leishmaniasis in endemic areas in Ecuador.

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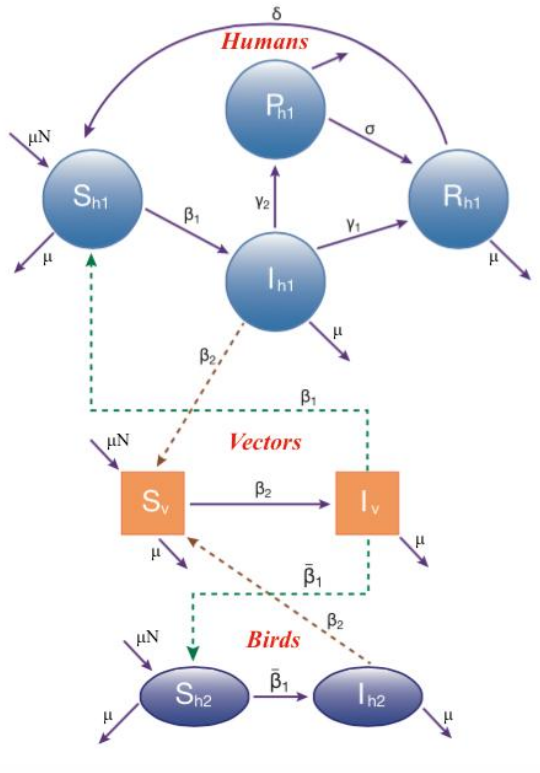
APPENDIX

Figure 1. Compartmental model flow chart with variables description.



Compartment	*Definition*
N_{h_1}	Total human population
S_{h_1}	Susceptible human population
I_{h_1}	Infected human population
P_{h_1}	Reported cases
R_{h_1}	Recovered human population
N_v	Sandflies population
S_v	Susceptible sandflies population
I_v	Infected sandflies population
N_{h_2}	Birds population
S_{h_2}	Susceptible birds population
I_{h_2}	Infected birds population

Figure 2. Distribution of R_0 from uncertainty quantification via fitting procedure. The estimated R_0 value is 3.9.

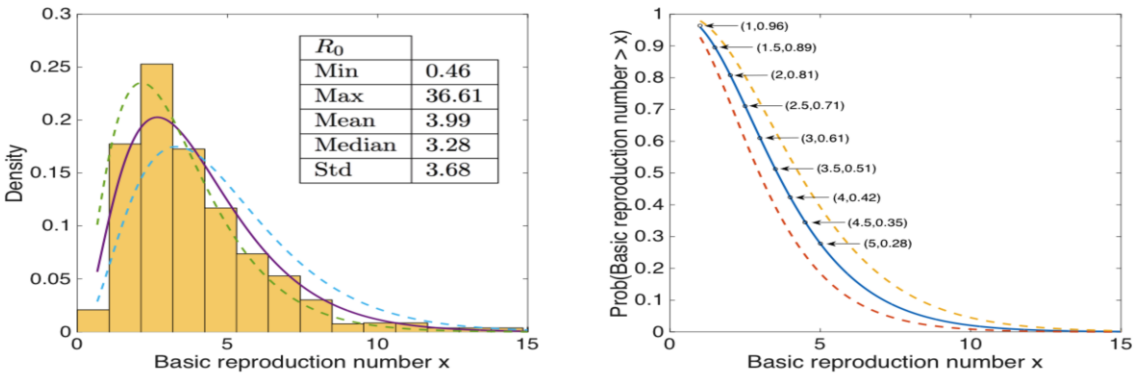


Table 1. Parameter and values of parameters used in our calculations.

Parameter	Parameter description	Value	Units	Source
μ_{h1}	Per capita human natural mortality rate in the coastal	$\frac{1}{26973.5}$	$days^{-1}$	(INEC, 2010)
b	Biting rate	0.2856	day^{-1}	(Elmojtaba, Mugisha, & Hashim, 2010)
β_1	Probability of successful transmission of infection from vector to human host given a bite	0.08223	$unitless$	(Anaguano, Ponce, Baldeón, Santander, & Cevallos, 2015a)
$\widetilde{\beta_1}$	Probability if successful transmission of infection from bird to vector given a bite	0.31399	$unitless$	(Anaguano et al., 2015a)
β_2	Probability of effective transmission from human host to a vector given a bite	0.25	$unitless$	(Bathena, 2009)
α_v	Level of feeding preference on human host	0.7924	$unitless$	(Anaguano et al., 2015b)
δ	Per capita rate immunity lost	0.0033	day^{-1}	(Bathena, 2009)
$\frac{1}{\gamma_1}$	Mean infections period	$\frac{1}{450}$	day^{-1}	(Cárdenas, 2014)
$\frac{1}{\gamma_2}$	Mean infectious period before reporting	$\frac{1}{15}$	$days^{-1}$	(Cárdenas, 2014)
$\frac{1}{\sigma}$	Percapita recovery rate with treatment	$\frac{1}{45}$	day^{-1}	(Cárdenas, 2014)

Table 2. Numerical estimates in decreasing order of importance respect to $\boldsymbol{R_0}$.

$\alpha_v \approx 0.93$

$u_{h1} \approx -0.93$

$\beta_2 = \frac{1}{2}$

$\widetilde{\beta_1} \approx 0.49$

$u_{h2} \approx 0.43$

$\beta_1 \approx 4.97763 * 10^{-5}$

$\gamma_2 \approx -1.60569 * 10^{-6}$

Calculations

Basic reproduction number

We can write our model, described in Figure 1, using the following system of ordinary differential equations:

$$S_{h1}^{'} = u_{h1}N_{h1} - \left(\frac{b\beta_1 I_v}{\alpha_v N_{h2} + N_{h1}}\right) S_{h1} + \delta R_{h1} - \mu_{h1} S_{h1}$$

$$I_{h1}^{'} = \left(\frac{b\beta_1 I_v}{\alpha_v N_{h2} + N_{h1}}\right) S_{h1} - \gamma_1 I_{h1} - \gamma_2 I_{h1} - \mu_{h1} I_{h1}$$

$$P_{h1}^{'} = \gamma_2 I_{h1} - \sigma P_{h1} - \mu_{h1} P_{h1}$$

$$R_{h1}^{'} = \gamma_1 I_{h1} + \sigma P_{h1} - \delta R_{h1} - \mu_{h1} R_{h1}$$

Humans

$$S_v^{'} = u_v N_v - \frac{b\beta_2(\alpha_v I_{h2} + I_{h1})}{\alpha_v N_{h2} + N_{h1}} S_v - \mu_v S_v$$

$$I_v^{'} = \frac{b\beta_2(\alpha_v I_{h2} + I_{h1})}{\alpha_v N_{h2} + N_{h1}} S_v - \mu_v I_v$$

Vectors

$$S_{h2}^{'} = u_{h2}N_{h2} - \left(\frac{b\widetilde{\beta_1} I_v}{\alpha_v N_{h2} + N_{h1}}\right) \alpha_v S_{h2} - \mu_{h2} S_{h2}$$

$$I_{h2}^{'} = \left(\frac{b\widetilde{\beta_1} I_v}{\alpha_v N_{h2} + N_{h1}}\right) \alpha_v S_{h2} - \mu_{h2} I_{h2}$$

Birds

In order to calculate the basic reproduction number we use the next generation matrix method [30]. Then, from our model (3) we consider the vector of new infection rates and the vector of all other rates.

$$\mathcal{F} = \begin{pmatrix} \left(\frac{b\beta_1 I_v}{\alpha_v N_{h2} + N_{h1}}\right) S_{h1} \\ 0 \\ \frac{b\beta_2(\alpha_v I_{h2} + I_{h1})}{\alpha_v N_{h2} + N_{h1}} S_v \\ \left(\frac{b\widetilde{\beta_1}\alpha_v I_v}{\alpha_v N_{h2} + N_{h1}}\right) S_{h2} \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\gamma_1 + \gamma_2 + \mu_{h1}) I_{h1} \\ -\gamma_2 I_{h1} + (\sigma + \mu_{h1}) P_{h1} \\ \mu_v I_v \\ \mu_{h2} I_{h2} \end{pmatrix}$$

Then the derivatives of these vector fields are

$$\mathcal{DF} = \begin{pmatrix} 0 & 0 & \frac{b\beta_1 S_{h1}}{\alpha_v N_{h2}+N_{h1}} & 0 \\ 0 & 0 & 0 & 0 \\ \frac{b\beta_2 S_v}{\alpha_v N_{h2}+N_{h1}} & 0 & 0 & \frac{b\beta_2 \alpha_v S_v}{\alpha_v N_{h2}+N_{h1}} \\ 0 & 0 & \frac{b\widetilde{\beta_1}\alpha_v S_{h2}}{\alpha_v N_{h2}+N_{h1}} & 0 \end{pmatrix}$$

$$\mathcal{DV} = \begin{pmatrix} \gamma_1+\gamma_2+\mu_{h1} & 0 & 0 & 0 \\ -\gamma_2 & \sigma+\mu_{h1} & 0 & 0 \\ 0 & 0 & \mu_v & 0 \\ 0 & 0 & 0 & \mu_{h2} \end{pmatrix}$$

Now we evaluate in the disease free equilibrium point (1) and we obtain:

$$F = \begin{pmatrix} 0 & 0 & \frac{b\beta_1 N_{h1}}{\alpha_v N_{h2}+N_{h1}} & 0 \\ 0 & 0 & 0 & 0 \\ \frac{b\beta_2 N_v}{\alpha_v N_{h2}+N_{h1}} & 0 & 0 & \frac{b\beta_2 \alpha_v N_v}{\alpha_v N_{h2}+N_{h1}} \\ 0 & 0 & \frac{b\widetilde{\beta_1}\alpha_v N_{h2}}{\alpha_v N_{h2}+N_{h1}} & 0 \end{pmatrix}$$

And

$$V = \begin{pmatrix} \gamma_1+\gamma_2+\mu_{h1} & 0 & 0 & 0 \\ -\gamma_2 & \sigma+\mu_{h1} & 0 & 0 \\ 0 & 0 & \mu_v & 0 \\ 0 & 0 & 0 & \mu_{h2} \end{pmatrix}$$

It is easy to see that

$$V^{-1} = \begin{pmatrix} \frac{1}{\gamma_1+\gamma_2+\mu_{h1}} & 0 & 0 & 0 \\ \frac{\gamma_2}{(\gamma_1+\gamma_2+\mu_{h1})(\sigma+\mu_{h1})} & \frac{1}{\sigma+\mu_{h1}} & 0 & 0 \\ 0 & 0 & \frac{1}{\mu_v} & 0 \\ 0 & 0 & 0 & \frac{1}{\mu_{h2}} \end{pmatrix}$$

Then the next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2} + N_{h1})\mu_v} & 0 \\ 0 & 0 & 0 & 0 \\ \frac{1}{\sigma + \mu_{h1}} & 0 & 0 & \frac{b\beta_2 \alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})\mu_v} \\ 0 & 0 & \frac{b\widetilde{\beta_1} \alpha_v N_{h2}}{(\alpha_v N_{h2} + N_{h1})\mu_v} & 0 \end{pmatrix}$$

Now, let´s calculate the eigenvalues of FV^{-1}

$$|FV^{-1} - \lambda I|$$

$$= \begin{vmatrix} -\lambda & 0 & \frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2} + N_{h1})\mu_v} & 0 \\ 0 & -\lambda & 0 & 0 \\ \frac{b\beta_2 \alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})(\gamma_1 + \gamma_2 + \mu_{h1})} & 0 & -\lambda & \frac{b\beta_2 \alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})\mu_{h2}} \\ 0 & 0 & \frac{b\widetilde{\beta_1} \alpha_v N_{h2}}{(\alpha_v N_{h2} + N_{h1})\mu_v} & -\lambda \end{vmatrix}$$

$$|FV^{-1} - \lambda I| = -\lambda \begin{vmatrix} -\lambda & \frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2} + N_{h1})\mu_v} & 0 \\ \frac{b\beta_2 N_v}{(\alpha_v N_{h2} + N_{h1})(\gamma_1 + \gamma_2 + \mu_{h1})} & -\lambda & \frac{b\beta_2 \alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})\mu_{h2}} \\ 0 & \frac{b\widetilde{\beta_1} \alpha_v N_{h2}}{(\alpha_v N_{h2} + N_{h1})\mu_v} & -\lambda \end{vmatrix}$$

$$= -\lambda \left\{ -\lambda^3 + \lambda \left(\frac{b\beta_2 N_v}{(\alpha_v N_{h2} + N_{h1})(\gamma_1 + \gamma_2 + \mu_{h1})} \right) \left(\frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2} + N_{h1})\mu_v} \right) + \left(\frac{b\widetilde{\beta_1} \alpha_v N_{h2}}{(\alpha_v N_{h2} + N_{h1})\mu_v} \right) \left(\frac{b\beta_2 \alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})\mu_{h2}} \right) \right\}$$

$$= \lambda^2 \left\{ \lambda^2 - \left(\frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2} + N_{h1})\mu_v} \right) \left(\frac{b\beta_2 N_v}{(\alpha_v N_{h2} + N_{h1})(\gamma_1 + \gamma_2 + \mu_{h1})} \right) - \left(\frac{b\widetilde{\beta_1} \alpha_v N_{h2}}{(\alpha_v N_{h2} + N_{h1})\mu_v} \right) \left(\frac{b\beta_2 \alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})\mu_{h2}} \right) \right\}$$

Then, the basic reproduction number for our model is

$$R_0^2 = \left(\frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2} + N_{h1})\mu_v}\right)\left(\frac{b\beta_2 N_v}{(\alpha_v N_{h2} + N_{h1})(\gamma_1 + \gamma_2 + \mu_{h1})}\right) + \left(\frac{b\widetilde{\beta_1}\alpha_v N_{h2}}{(\alpha_v N_{h2} + N_{h1})\mu_v}\right)\left(\frac{b\beta_2\alpha_v N_v}{(\alpha_v N_{h2} + N_{h1})\mu_{h2}}\right)$$

Existence of an Endemic Equilibrium Point

Assuming that populations are constant in our system we can write

$S_{h1} = N_{h1} - I_{h1} - P_{h1} - R_{h1}$, $S_v = N_v - I_v$, and $S_{h2} = N_{h2} - I_{h2}$

Then, in order to calculate the endemic equilibrium point we have to solve the equations

(4) $\Lambda_v\beta_1 I_v(N_{h1} - I_{h1} - P_{h1} - R_{h1}) - (\gamma_1 + \gamma_2 + \mu_{h1})I_{h1} = 0$

(5) $\gamma_2 I_{h1} - (\sigma + \mu_{h1})P_{h1} = 0$

(6) $\gamma_1 I_{h1} + \sigma P_{h1} - (\delta + \mu_{h1})R_{h1} = 0$

(7) $\Lambda_v\beta_2(\alpha_v I_{h2} + I_{h1})(N_v - I_v) - \mu_v I_v = 0$

(8) $\Lambda_v\widetilde{\beta_1}\alpha_v I_v(N_{h2} - I_{h2}) - \mu_{h2} I_{h2} = 0$

Where $\Lambda_v = \frac{b}{(\alpha_v N_{h2} + N_{h1})}$

From equations (4) and (5) we have

$P_{h1} = \frac{\gamma_2}{(\sigma + \mu_{h1})I_{h1}}$ and $R_{h1} = \frac{\gamma_1\sigma + \gamma_1\mu_{h1} + \gamma_2\sigma}{(\sigma + \mu_{h1})(\delta + \mu_{h1})} I_{h1}$ (9)

And from equation (8) we obtain

$I_v = \frac{\mu_{h2} I_{h2}}{\Lambda_v\widetilde{\beta_1}\alpha_v(N_{h2} - I_{h2})}$ (10)

Now, using these three last equations and equation (5) we obtain

$$\frac{\beta_1\mu_{h2}I_{h2}}{\widetilde{\beta_1}\alpha_v\,(N_{h2}-I_{h2})}\left(N_{h1}-I_{h1}-\frac{\gamma_2}{(\,\sigma+\mu_{h1})}\,I_{h1}-\frac{\gamma_1\sigma+\gamma_1\mu_{h1}+\gamma_2\sigma}{(\,\sigma+\mu_{h1})(\delta+\mu_{h1}\,)}I_{h1}\right)-(\gamma_1+\gamma_2+\mu_{h1})I_{h1}=0,$$

Therefore,

$$I_{h1}=\frac{\beta_1\mu_{h2}N_{h1}I_{h2}}{\beta_1\mu_{h2}\left(1+\frac{\gamma_2}{(\sigma+\mu_{h1})}+\frac{\gamma_1\sigma+\gamma_1\mu_{h1}+\gamma_2\sigma}{(\,\sigma+\mu_{h1})(\delta+\mu_{h1}\,)}\right)I_{h2}+\widetilde{\beta_1}\alpha_v\,(\gamma_1+\gamma_2+\mu_{h1})(N_{h2}-I_{h2})}$$

If we can guarantee that I_{h2} is positive we will have I_{h1} positive too. In order to do that we use equations (10) and (7), then we arrive in the following quadratic equation

$$(\Lambda_v b\beta_2\widetilde{\beta_1}{\alpha_v}^2N_v+b\beta_2\alpha_v\,\mu_{h2})I_{h2}{}^2-\Big(\Lambda_v b{\alpha_v}^2\beta_2\widetilde{\beta_1}N_vN_{h2}-\Lambda_v b\beta_2\widetilde{\beta_1}\alpha_v\,N_vI_{h1}-$$

$$b\beta_2\mu_{h2}I_{h1}-\mu_v\mu_{h2}(\alpha_v\,N_{h2}+N_{h1})\Big)\,I_{h2}-\Lambda_v b\beta_2\widetilde{\beta_1}\alpha_v\,N_vN_{h2}I_{h1}=0$$

(12)

The last coefficient of this equation is negative and the first one is positive which implies the equation has two real roots, one negative and one positive. This proves that our model has one endemic equilibrium point.

Special case I: Reduced Model without reporting

$$S_{h1}^{'}=u_{h1}N_{h1}-\left(\frac{b\beta_1I_v}{\alpha_vN_{h2}+N_{h1}}\right)S_{h1}+\delta R_{h1}-\mu_{h1}S_{h1}$$

$$I_{h1}^{'}=\left(\frac{b\beta_1I_v}{\alpha_vN_{h2}+N_{h1}}\right)S_{h1}-\gamma_1I_{h1}-\mu_{h1}I_{h1}$$

$$R_{h1}^{'}=\gamma_1I_{h1}-\ \delta R_{h1}-\mu_{h1}R_{h1}$$

Humans

$$S_v^{'}=u_vN_v-\frac{b\beta_2(\alpha_v\,I_{h2}+I_{h1})}{\alpha_v\,N_{h2}+N_{h1}}S_v-\mu_vS_v$$

$$I_v^{'}=\frac{b\beta_2(\alpha_v\,I_{h2}+I_{h1})}{\alpha_v\,N_{h2}+N_{h1}}S_v-\mu_vI_v$$

Vectors

$$S_{h2}^{'} = u_{h2}N_{h2} - \left(\frac{b\widetilde{\beta_1}I_v}{\alpha_v N_{h2}+N_{h1}}\right)\alpha_v S_{h2} - \mu_{h2}S_{h2}$$

$$I_{h2}^{'} = \left(\frac{b\widetilde{\beta_1}I_v}{\alpha_v N_{h2}+N_{h1}}\right)\alpha_v S_{h2} - \mu_{h2}I_{h2}$$

Birds

The basic reproductive number for this model is given by

$$R_0^2 = \left(\frac{b\beta_1 N_{h1}}{(\alpha_v N_{h2}+N_{h1})\mu_v}\right)\left(\frac{b\beta_2 N_v}{(\alpha_v N_{h2}+N_{h1})(\gamma_1+\mu_{h1})}\right)$$

$$+\left(\frac{b\widetilde{\beta_1}\alpha_v N_{h2}}{(\alpha_v N_{h2}+N_{h1})\mu_v}\right)\left(\frac{b\beta_2\alpha_v N_v}{(\alpha_v N_{h2}+N_{h1})\mu_{h2}}\right)$$

Special case II: Reduced Model without bird reservoir hosts

$$S_{h1}^{'} = u_{h1}N_{h1} - b\beta_1 S_{h1}\left(\frac{I_v}{N_{h1}}\right) + \delta R_{h1} - \mu_{h1}S_{h1}$$

$$I_{h1}^{'} = b\beta_1 S_{h1}\left(\frac{I_v}{N_{h1}}\right) - \gamma_1 I_{h1} - \gamma_2 I_{h1} - \mu_{h1}I_{h1}$$

$$P_{h1}^{'} = \gamma_2 I_{h1} - \sigma P_{h1} - \mu_{h1}P_{h1}$$

$$R_{h1}^{'} = \gamma_1 I_{h1} + \sigma P_{h1} - \delta R_{h1} - \mu_{h1}R_{h1}$$

Humans

$$S_v^{'} = u_v N_v - b\beta_2 S_v\left(\frac{I_{h1}}{N_{h1}}\right) - \mu_v S_v$$

$$I_v^{'} = b\beta_2 S_v\left(\frac{I_{h1}}{N_{h1}}\right) - \mu_v I_v$$

Vectors

The basic reproduction number for this model is given by

$$R_0^2 = \left(\frac{b\beta_1}{\mu_v}\right)\left(\frac{b\beta_2 N_v}{N_{h1}(\gamma_1+\gamma_2+\mu_{h1})}\right) \qquad (14)$$

Special case III: Reduced Model without reporting

$$S_{h1}^{'} = u_{h1}N_{h1} - b\beta_1 S_{h1}\left(\frac{I_v}{N_{h1}}\right) + \delta R_{h1} - \mu_{h1}S_{h1}$$

$$I_{h1}^{'} = b\beta_1 S_{h1}\left(\frac{I_v}{N_{h1}}\right) - \gamma_1 I_{h1} - \mu_{h1}I_{h1}$$

$$R_{h1}^{'} = \gamma_1 I_{h1} + \sigma P_{h1} - \delta R_{h1} - \mu_{h1}R_{h1}$$

Humans

$$S_v^{'} = u_v N_v - b\beta_2 S_v\left(\frac{I_{h1}}{N_{h1}}\right) - \mu_v S_v$$

$$I_v^{'} = b\beta_2 S_v\left(\frac{I_{h1}}{N_{h1}}\right) - \mu_v I_v$$

Vectors

Then, in this case the basic reproductive number is

$$R_0^2 = \left(\frac{b\beta_1}{\mu_v}\right)\left(\frac{b\beta_2 N_v}{N_{h1}(\gamma_1+\mu_{h1})}\right) \qquad (15)$$

Using the software Mathematica

$$E^* = (S_{h1}^*, I_{h1}^*, R_{h1}^*, S_v^*, I_v^*)$$

$$S_{h1}^* = \frac{{N_{h1}}^2(\gamma_1+\mu_{h1})(b\beta_2(\delta+\mu_{h1}) + \mu_v(\gamma_1+\delta+\mu_{h1}))}{b\beta_2(b\beta_1 N_v(\gamma_1+\delta+\mu_{h1}) + N_{h1}(\gamma_1+\mu_{h1})(\delta+\mu_{h1}))} > 0$$

$$I_{h1}^{*} = \frac{N_{h1}(\delta + \mu_{h1})(b^2\beta_1\beta_2 N_v - N_{h1}\mu_v(\gamma_1 + \mu_{h1}))}{b\beta_2(b\beta_1 N_v(\gamma_1 + \delta + \mu_{h1}) + N_{h1}(\gamma_1 + \mu_{h1})(\delta + \mu_{h1}))}$$

$$= \frac{{N_{h1}}^2\mu_v(\delta + \mu_{h1})(\gamma_1 + \mu_{h1})(R_0^2 - 1)}{b\beta_2(b\beta_1 N_v(\gamma_1 + \delta + \mu_{h1}) + N_{h1}(\gamma_1 + \mu_{h1})(\delta + \mu_{h1}))} > 0, \qquad if\ R_0 > 1$$

$$R_{h1}^{*} = \frac{\gamma_1 N_{h1}(b^2\beta_1\beta_2 N_v - N_{h1}\mu_v(\gamma_1 + \mu_{h1}))}{b\beta_2(b\beta_1 N_v(\gamma_1 + \delta + \mu_{h1}) + N_{h1}(\gamma_1 + \mu_{h1})(\delta + \mu_{h1}))}$$

$$= \frac{\gamma_1{N_{h1}}^2\mu_v(\gamma_1 + \mu_{h1})({R_0}^2 - 1)}{b\beta_2(b\beta_1 N_v(\gamma_1 + \delta + \mu_{h1}) + N_{h1}(\gamma_1 + \mu_{h1})(\delta + \mu_{h1}))} > 0, \qquad if\ R_0 > 1$$

$$S_v^{*} = \frac{\mu_v(b\beta_1 N_v\,(\gamma_1 + \delta + \mu_{h1}) + N_{h1}(\gamma_1 + \mu_v)(\delta + \mu_{h1}))}{b\beta_1(b\beta_2\,(\delta + \mu_{h1}) + \mu_v(\gamma_1 + \delta + \mu_{h1}))} > 0$$

$$I_v^{*} = \frac{(\delta + \mu_{h1})(b^2\beta_1\beta_2 N_v - N_{h1}\mu_v(\gamma_1 + \mu_{h1}))}{b\beta_1(b\beta_2\,(\delta + \mu_{h1}) + \mu_v(\gamma_1 + \delta + \mu_{h1}))}$$

$$= \frac{(\delta + \mu_{h1})\,N_{h1}\mu_v(\gamma_1 + \mu_{h1})({R_0}^2 - 1)}{b\beta_1(b\beta_2\,(\delta + \mu_{h1}) + \mu_v(\gamma_1 + \delta + \mu_{h1}))} > 0, \qquad if\ \ R_0 > 1$$

Weighted Least Squares

Let $\vec{\theta} = (\beta_1, \beta_2, \gamma_3)^T \in R_+^2$ be a vector

$f(t;\ \vec{\theta})\ \int_0^t \frac{b\beta_1 I_v(\tau;\vec{\theta})}{\alpha_v N_{h2}(\tau;\vec{\theta}) + N_{h1}(\tau;\vec{\theta})}\ S_{h1}(\tau;\vec{\theta})\,d\tau$

The 2011 epidemiological data fitting

$$y_i = f(t_i;\overrightarrow{\theta_0}) + f(t_i;\overrightarrow{\theta_0})^{\xi}\epsilon_i, \quad for\ \ i = 1, \dots, n$$

Where $\overrightarrow{\theta_0}$ is the vector ….

$$J_n(\overrightarrow{\theta_0}) = \sum_{i=1}^{n} \widehat{w_i} \, |y_i - f(t_i; \vec{\theta})|^2$$

Where the weights $\widehat{w_i}$, are given by

$$\widehat{w_i} = (f(t_i; \vec{\theta}))^{-1}, \quad for\ i = 1, \dots, n$$

Sensitivity Indexes of R_0

The normalized sensitivity index S_{u_p} is defined to be ratio

$$S_{u_p} \coloneqq \lim_{\delta p \to 0} \left(\frac{\delta u}{u}\right)\left(\frac{\delta p}{p}\right)^{-1} = \frac{p}{u}\,\frac{\delta u}{\delta p}$$

Provided $u \neq 0$ (If $u = 0$ we modify the SI to be $\frac{p}{u+1}\frac{\delta u}{\delta p}$). The practical meaning of S_{u_p}

$$SI_{\beta_1} = \frac{\beta_1 \mu_{h2} N_{h1}}{2\widetilde{\beta_1}\, N_{h2}\, \alpha_v^2(\gamma_1 + \gamma_2 + \mu_{h1}) + 2\beta_1 \mu_{h2} N_{h1}}$$

$$SI_{\beta_2} = \frac{1}{2} > 0, \qquad SI_{u_v} = -\frac{1}{2} < 0$$

$$SI_{\mu_{h2}} = -\frac{\widetilde{\beta_1} N_{h2}\, \alpha_v{}^2(\gamma_1 + \gamma_2 + \mu_{h1})}{2\left(\widetilde{\beta_1} N_{h2}\, \alpha_v{}^2(\gamma_1 + \gamma_2 + \mu_{h1}) + \beta_1 \mu_{h2} N_{h1}\right)} \approx -.5$$

$$SI_{\widetilde{\beta_1}} = \frac{\widetilde{\beta_1} N_{h2}\, \alpha_v{}^2(\gamma_1 + \gamma_2 + \mu_{h1})}{2\,\widetilde{\beta_1} N_{h2}\, \alpha_v{}^2(\gamma_1 + \gamma_2 + \mu_{h1}) + 2\beta_1 \mu_{h2} N_{h1}}$$

$$SI_{\gamma_1} = -\frac{\beta_1 \gamma_1 \mu_{h2} N_{h1}}{2\,(\gamma_1 + \gamma_2 + \mu_{h1})(\,\widetilde{\beta_1} N_{h2}\, \alpha_v{}^2(\gamma_1 + \gamma_2 + \mu_{h1}) + \beta_1 \mu_{h2} N_{h1})}$$