



# Uncertainty and sensitivity analysis of a Rift Valley fever model



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## ABSTRACT

Rift Valley fever (RVF) is a vector-borne viral disease with pronounced health and economic impacts on domestic animals and humans in much of sub-Saharan Africa. Using techniques of uncertainty and sensitivity analysis (both local derivatives and sampling-based methods) of a mathematical model for RVF transmission in livestock by two population of mosquitoes (*Aedes* and *Culex*). We systematically investigate the relative importance of each model parameter for both disease epidemic and endemic activities. The relationship between vertical transmission and basic reproduction number reveals that during epidemic activities vertical transmission accelerates the course of the outbreak as it increases the size of infected vectors and reduces the duration of the outbreak. However, during endemic activities, vertical transmission exceeding 20% highly influences the basic reproduction number and disease persistence. Results of both local and global sensitivity analysis agrees that  $R_0$  is most sensitive to vertical transmission, probability of transmission from *Aedes* mosquitoes to host, vector initial density and number of bites an *Aedes* mosquito would want to bite a host and number of bites that a host can sustain. This suggests that reducing vector population and enhancing control intervention in livestock is a viable preventive strategy. Both time varying and time invariant sensitivity analysis of disease prevalence governed by both asymptomatic and symptomatic state variables indicate that the most significant parameters are: number of bites that an *Aedes* mosquito would want to bite a host, number of bites a host can sustain, probability of transmission from host to an *Aedes* mosquito and the host death rate. Furthermore, time varying sensitivity analysis provides a comprehensive overview of the effects of each model input parameter at all important stages of the epidemic.

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## 1. Introduction

Rift Valley fever (RVF) is a vector-borne viral disease caused by RVF virus (RVFV) belonging to the genus *Phlebovirus* of the family *Bunyaviridae* [1]. The virus infects primarily both wild and domestic animals, however it is also capable of infecting humans. In animals, infection can produce high rates of abortion and significant morbidity and mortality [2]. Animal loss

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can lead to food shortages, loss of earnings and livelihoods with devastating economic impacts, particularly in vulnerable African communities with low resilience to economic and environmental challenges [3,4]. The 2006–07 RVF outbreak in East Africa was the most widespread with total number of deaths of 16,973 in cattle, 20,193 in goats and 12,124 in sheep resulting in economic losses amounting to US \$32 million in Kenya alone [5]. The disease is endemic in much of sub-Saharan Africa [6] with significant differences in the ecology and epidemiology of the disease. The disease occurs in two distinct cycles: the enzootic/endemic and the epizootic/epidemic cycles [7]. The enzootic transmission occurs at low levels in nature during periods of average rainfall (low moisture) in which the virus is maintained through vertical transmission from the female *Aedes* mosquito to eggs and through occasional amplification cycles in susceptible livestock [3,8]. The epizootic cycle appears at irregular intervals of 5 to 15 years, after heavy rainfall and floods (high moisture), which stimulate the hatching of infected *Aedes* mosquito eggs, resulting in a massive emergence of *Aedes* with subsequent elevation of various *Culex* species that serve as the amplifiers of the disease [7,9].

Vector control in either adult or mosquito larvae and livestock vaccination are among the most effective disease control and public health intervention measures. However, the effectiveness of any intervention program depends mainly in our knowledge of disease transmission, threshold concept in the epidemiology of the disease and disease parameters that govern its spread. The basic reproduction,  $R_0$  is one of the foremost concepts in the epidemiology of the disease [10], which is widely used to quantify the spread of the disease at early stage of the epidemic. This quantity is either derived from data or from mathematical models that describe the dynamics of the disease. Mathematical models consist of parameters and initial conditions for independent and dependent variables. In most cases these parameters are not known with sufficient degree of certainty due to natural variations and error in measurements [11].

Uncertainty and sensitivity analysis of model parameters is very important for quantifying these variations and uncertainties. For example, sensitivity analysis enhances our understanding and guide in developing appropriate measures for disease control. Uncertainty analysis is used to explore the uncertainty in the model output that is generated from uncertainty in input parameters [11] while sensitivity analysis assesses how variations in model outputs can be attributed qualitatively and quantitatively to different input parameters [12]. Although the field of mathematical epidemiology is well established very few models of RVF have been developed and analysed. This is in part due to the fact that the disease for many years was known as a disease of animals only. Thus, receiving little attention from various stakeholders. In the recent past few RVF mathematical models have been developed, see [13–19] and references therein. However, only few studies have performed uncertainty and sensitivity analysis of RVF epidemic models to the parameters and to the endemic equilibrium state [13–15,17]. These studies have determined the relative importance of various parameters in RVF transmission and spread characterised by  $R_0$  using sampling-based uncertainty and sensitivity analysis techniques, with exception of Mpeshe et al. [14] who applied sensitivity indices of the endemic equilibrium point to the model parameters. Still, two main questions remain not completely explored: (1) what is the role and contribution of vertical transmission from *Aedes* mosquitoes for both disease epidemic and endemic activities? (2) What is the time contribution of each model parameters to model output variations during an outbreak? The former question is central to our understanding of the relative importance of various input parameters as the disease evolve with time. The same input model parameter may contribute to model output variations in different ways as the model evolves with time. That is, for instance at the beginning of an outbreak the parameter may be positively correlated to the size of the epidemic but at the peak of the outbreak this correlation may inverse [11]. To the best of our knowledge these types of analyses are missing in disease models, particularly to vector-borne disease models such as RVF models.

Therefore, in this paper we use our previous RVF model [19] to systematically study the sensitivity of both the measure of the initial spread of the disease,  $R_0$  and the measure of disease prevalence, represented by the endemic equilibrium state,  $E^*$  to both low and high moisture model parameters. The initial spread of the disease depends on the competence of primary vectors, the *Aedes* mosquitoes through vertical transmission [19]. Hence, we start our analysis by investigating the relative importance of vertical transmission in disease transmission and persistence. Then we proceed with sensitivity analysis of the basic reproduction number,  $R_0$  using two approaches: one based on local derivatives and the other on sampling-based method, that is, Latin hypercube sampling (LHS) on combination with partial rank correlation coefficient (PRCC). Furthermore, we perform uncertainty and sensitivity analysis of some chosen model state variables (Uninfected eggs,  $U_1$ , Exposed *Aedes*  $E_1$ , Infected *Aedes*  $I_1$ , Infected symptomatic host  $A_2$ , Infected symptomatic host  $I_2$ , Exposed *Culex*  $E_3$  and Infected *Culex*  $I_3$ ) to model input parameters at a particular time during the course of the outbreak. In addition, we compute the sensitivity indices of the endemic equilibrium state,  $E^*$  using local derivatives in order to assess the relative importance of different input parameters to disease prevalence. Finally, in order to assess whether significance of each parameter occurs over an entire time interval during model dynamics, we investigate the rank correlation coefficient (RCCs) for multiple time points and plot them versus time. We show that during endemic cycle (low moisture) vertical transmission drives the persistence of the disease. In addition, a threshold of this rate is required for virus reproduction and subsequent propagation. However, during periods of outbreaks (high moisture) the effect of vertical transmission is significant in the first transmission cycle and may actually reduce the time of the outbreak. Our analysis sheds new light on the relative importance of the most significant input parameter for both disease epidemic and endemic/inter-epidemic activities for both single and multiple time points. Time varying sensitivity analysis provides to our understanding deep insights about how each parameter contributes to disease dynamics at every important stage of the epidemic which is central for designing appropriate intervention strategies.

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