frontiers

Population dynamics of Rift Valley fever virus: effects of live and killed vaccines on epizootic outbreaks and enzootic maintenance

Farida Chamchod[1], **Chris Cosner**[2], **Robert Stephen Cantrell**[2], **John C. Beier**[3] **and Shigui Ruan**[2,*]

[1] *Department of Mathematics, Faculty of Science, Mahidol University, Bangkok 10400, Thailand*
[2] *Department of Mathematics, University of Miami, Coral Gables, FL 33146, USA*
[3] *Department of Public Health Sciences, Miller School of Medicine, University of Miami, Miami, FL 33136, USA*

Correspondence*:
Shigui Ruan
Department of Mathematics, Coral Gables, Miami, FL 33146, USA,
ruan@math.miami.edu

ABSTRACT

Rift Valley fever virus (RVFV) is an arthropod-borne viral pathogen that causes significant morbidity and mortality among ruminants throughout Africa and the Middle East. Vaccination is an important means to reduce the risk of RVFV infection in the ruminant population but has proved to be challenging due to the sporadic and explosive nature of RVF outbreaks; currently, two types of vaccines, live and killed, are available in endemic areas. Two modeling approaches have been developed in this study to explore the impact of vaccination via live versus killed vaccines on the transmission dynamics of RVFV. We demonstrate in general that vaccination helps reduce the severity of RVF outbreaks and that less delay in implementation and more effective vaccines can reduce the outbreak magnitude and the prevalence of RVFV. However, an introduction of a number of ruminants vaccinated by live vaccines in RVFV-free areas may cause an outbreak and RVFV may become endemic if there is sustained use of live vaccines. Moreover, unsustained vaccination programs and the increase of susceptibility in the ruminant population may lead to the recurrence of RVF outbreaks. The abundance of mosquitoes is one of the important determinants of the onset of RVF outbreaks. We show that the higher the number of mosquitoes, the more severe the outbreak, and in endemic areas annual RVF cases may fluctuate according to seasonal abundance of mosquitoes. Furthermore, recruiting susceptible ruminants during high mosquito activity may increase the risk of outbreaks and the risk is higher in areas where live vaccines are used for preventive control. Our models predict that the risk of outbreaks is also increased by vaccinating ruminants with live vaccines during periods of high mosquito activity but vaccination is recommended if the period with high mosquito activity is longer than the period with low mosquito activity.

Keywords: Rift Valley fever, Transmission Dynamics, Live vaccine, Killed vaccine, Seasonality Forces

1 INTRODUCTION

Rift Valley fever virus (RVFV) is an arthropod-borne viral pathogen belonging to the *Phlebovirus* genus in the *Bunyaviridae* family that has a considerable effect on domesticated animals and humans in Africa and

the Middle East. The virus was first detected in 1930 in Kenya and initially confined to Africa including Egypt, which later moved into the Middle East in 2000 (**Abdo-Salem et al.** (2011b)). Infection with RVFV in animals is often associated with bloody diarrhea, necrotic hepatitis, hemorrhages, and abortions; the mortality rate in some species of ruminants is nearly 100% in young animals and approximately 20%-30% in adults; and the abortion rate of pregnant ruminants ranges from 40% to 100% during an outbreak (**Evans et al.** (2008); **McElroy et al.** (2009)). However, susceptibility of ruminants to RVFV infection varies among species of ruminants, breeds, ages, and viral strains; for example, sheep are more susceptible than cattle and infected camels have as low as 2% mortality rate and only occasional abortions (**Smith et al.** (2010); **Munyua et al.** (2010)). Humans infected with RVFV typically experience mild symptoms including fever, myalgia, and headache but 1%-3% of cases they may develop severe encephalitis, renal failure, fatal hepatitis, and hemorrhagic fever (**Näslund et al.** (2009); **Smith et al.** (2010)).

Transmission of RVFV among ruminants is primarily by vectors. Numerous species of mosquitoes may be able to transmit RVFV but *Aedes* and *Culex* are considered the main vectors (**Fontenille et al.** (1998); **Abdo-Salem et al.** (2011b)). Humans can be infected by mosquito bites, contact with or inhalation of aerosols during the handling or slaughtering of infected ruminants. RVF outbreaks are sporadic (outbreaks occur between 10 and 15 years or between 3 and 5 years in some endemic areas (**Andriamandimby et al.** (2010); **Nderitu et al.** (2011))). Outbreaks are often linked to the coincidence of heavy rainfall and flooding events that allow large numbers of mosquitoes to emerge and facilitate RVFV transmission, the presence of susceptible livestock, and the presence of RVFV (**El-Rahim et al.** (1999)). RVFV is associated with two distinct transmission cycles: low-level enzootic and epizootic (**Hollidge et al.** (2010)). During enzootic activities, when there is non-excessive rainfall, it is believed that in East Africa RVFV is maintained through vertical transovarial transmission of floodwater *Aedes* species especially in areas with shallow depression habitats or dambos (**Linthicum et al.** (1985, 1999)). High viremia in infected ruminants caused by transovarially infected *Aedes* mosquitoes that emerge from flooding events may allow the spillover of RVFV to secondary vectors such as *Culex* or *Anopheles* mosquitoes (**Bird** (2012)). Factors associated with epizootics in West Africa, high rain forest zones of coastal and Central Africa remain unknown and vertical transovarial transmission is not currently present in the Middle East and West Africa (**El-Rahim et al.** (1999); **Martin et al.**).

Because of the high number of competent vectors of RVFV, the intensification of international trade of live animals that may introduce infected ruminants into non-endemic areas with high densities of susceptible livestock, and the unknown impact of climate change, several national and international agencies have issued warnings of the heightened risk of RVFV introduction (**Ikegami and Makino** (2009); **Pepin et al.** (2010)). Typically, preventive measures to control the spread of RVFV include disease surveillance, strategic vaccination of livestock, intensive vector control, restriction of animal movement, bans on animal importation from RVF-endemic countries and increasing public awareness (**Al-Afaleq and Hussein** (2011)). Due to the severity and economic consequences of RVF outbreaks, routine immunization of lambs and calves is recommended and currently two types of vaccines are available in endemic areas for the prophylactic immunization of ruminants (**von Teichman et al.** (2011)). However, routine vaccination is prohibitively expensive in Africa and sustaining vaccination programs in ruminants between outbreaks has proved difficult (**Rusnak et al.** (2011)).

Live attenuated RVFV vaccines (or live vaccines) provide long-term protective immunity without booster inoculations and are inexpensive to produce. The vaccines were developed from the Smithburn strain of RVFV by serial passages in mouse brains (**Smithburn** (1949); **Ikegami and Makino** (2009)). As the neuroadapted virus only partially lost its virulence, this type of vaccine may induce abortions and teratogenesis in pregnant ruminants, and has the potential for reversion and capability to cause viraemia so that mosquitoes feeding on vaccinated ruminants may become infected and transmit RVFV to other ruminants and humans (**Ikegami and Makino** (2009); **Pepin et al.** (2010); **Kamal** (2011)). Consequently, live vaccines are restricted and only used during devastating outbreaks, cannot be used in pregnant and young ruminants, and are not recommended in countries where RVFV has not been yet introduced. Moreover, according to the vaccine description, they should not be administered to animals during breeding season of mosquitoes; animals used for human consumption should not be slaughtered

within 21 days after vaccination; and used syringes, needles and remaining vaccine in bottles should be disposed hygienically (**Kamal** (2011)).

Formalin-inactivated RVFV vaccines (or killed vaccines) can be administered to animals of all ages and are safe, but are not efficacious as live vaccines and require repeated immunizations to induce and maintain protective immunity since an initial dose may only immunize a ruminant for 6-12 months (**Ikegami and Makino** (2009)). These vaccines consist of relatively concentrated suspensions of the virulent virus that have been inactivated by formaldehyde or other chemical substances and hence would be suitable for use in non-endemic areas and in animals exported from endemic to RVFV-free areas (**Wolrld Health Organization** (1982); **von Teichman et al.** (2011)). Although killed vaccines have advantages of safety, they are costly to produce and difficult to store owing to poor stability over long periods of time (**Wolrld Health Organization** (1982)).

Clearly, the use of live and killed vaccines to control the spread of RVFV is hampered by their disadvantages and highly effective vaccines are needed. New generation vaccines are currently under development and under clinical trials: the attenuated MP12 which was derived from the virulent Egyptian strain (ZH548) and a plaque isolate of RVFV 74HB59, Clone 13, which is avirulent and not able to revert due to a large deletion in the NSs protein (that has been pointed out to be a virulence factor in animals), for instance (**Ikegami and Makino** (2009); **Pepin et al.** (2010); **Rusnak et al.** (2011)). A virus-like particle (VLP) approach and immunization with plasmids are examples of alternative approaches to develop vaccines (**Ikegami and Makino** (2009); **LaBeaud** (2010)). Effective vaccines surely will facilitate the preparedness for prevention of an introduction of RVFV to disease-free areas and help reduce economic losses from dead and aborted ruminants and transmission of RVFV. The ideal vaccine would be one that is safe without causing any pathogenic reaction and virulence reversion, confers long-term protection within a single dose, provides the ability to differentiate between naturally infected and vaccinated animals (DIVA), and is not expensive and difficult to produce (**LaBeaud** (2010)). Although vaccines can induce immunity against RVFV, it is important to recognize that recombination between live vaccinal strain and virulent strains is possible, and vaccines with deleted genes can reobtain those missing genes and cause serious consequences for disease elimination (**Kamal** (2011)).

Many modeling tools have been used to explore the risk of recurrent outbreaks in the endemic areas and the risk of RVF introduction in disease-free areas including climatic indices, spatial techniques, multivariable statistical analysis, and dynamical transmission models (see **Métras et al.** (2011) for a review). However, studies that use dynamical transmission models (**Favier et al.** (2006); **Bicout and Sabatier** (2004); **Gaff et al.** (2007); **Mpeshe et al.** (2011); **Xue et al.** (2012); **Gao et al.** (2013); **Chamchod et al.** (2014); **Xiao et al.** (2015)) are still scant and to our knowledge none of those preceding studies have addressed the use of live and killed vaccines in which clearly an important and currently used means to control RVF epizootics and enzootics. In this study, we develop two modeling approaches to investigate the transmission dynamics of RVFV and the impacts of using live or killed vaccines. These two novel frameworks that capture advantages and disadvantages of live and killed vaccines incorporate with several factors that may influence RVFV activities such as delay in vaccination, efficacy of vaccines, recruitment of animals, quarantine strategies, the abundance of mosquitoes, and vaccination strategies to explore severity of RVF outbreaks, the prevalence of RVFV, the recurrence of outbreaks and the virus introduction. Our study provides an important insight into the effects of implementation of live or killed vaccines as an RVF control measure and underline the need for effective vaccines, and possibly can be applied to explore certain other diseases for which live or killed vaccines are or may be used as preventive tools; West Nile virus, in which a number of candidates for live and killed vaccines are currently in various stages of testing, is a possible example (**Tesh et al.** (2002)).

2 METHODS

We begin by introducing vaccination models for live and killed vaccines. A ruminant population (N) is divided into susceptible (S), infectious (I), recovered (R) and vaccinated by live vaccines (V_1) or

Table 1. Lists of parameters for Rift Valley fever virus transmission

Description	Symbol	Sample value	References
Natural death rate in ruminants (year^{-1})	μ	1/5.7-1/2	**Majok et al.** (1991)
Birth rate in ruminants (year^{-1})	b	2.3	**Majok et al.** (1991)
Recovery duration (year)	τ	8/365	**Pepin et al.** (2010)
Probability of death due to RVFV in ruminants	m	0.3	**Evans et al.** (2008)
Rate of recovery in ruminants (year^{-1})	γ	$(1-m)(1/\tau)$	
RVF-related death rate in ruminants (year^{-1})	d	$m(1/\tau)$	
The maximum number of ruminants (reflecting limited resources)	N^0	100000	estimated
Crowding parameter of ruminants	q	$(b-\mu)/N^0$	
Proportion of surviving newborns from infectious ruminants	r_1	0.6	**McElroy et al.** (2009)
Proportion of surviving newborns from ruminants vaccinated by live vaccines	r_2	0.72	**Kamal** (2011)
Vaccination rate (year^{-1})	ϕ_1, ϕ_2	365/141	**Métras et al.** (2011)
Probability that ruminants are vaccinated	ρ_{11}, ρ_{21}	0-1, 0.8	(varying)
Probability of successfully acquiring immunity from live vaccines	ρ_{12}	0-1, 0.9	(varying)
Probability of reversion of virulence of live vaccines	ρ_{13}	0-0.2, 0.05	(varying)
Probability of receiving a repeated dose of killed vaccine	ρ_{22}	0-1, 0.8	(varying)
Duration of viraemia in ruminants vaccinated by live vaccines (year)	λ	365/21	**Kamal** (2011)
Duration of protection from a primary dose of killed vaccine (year)	ν	1/(5/12)	**Kamal** (2011)
Biting rate (year^{-1})	a	256	
Probability of successful infection in ruminants	p_r	0.14	**Turell et al.** (2008)
Probability of successful infection in mosquitoes	p_m	0.35	**Turell et al.** (2008)
Birth rate in mosquitoes (year^{-1})	g	73	**Dye** (1984); **Hancock et al.** (2009)
Death rate of mosquitoes (year^{-1})	η	365/60	**Reiskind et al.** (1987)
Maximum mosquito:ruminant ratio at	k_0	0-10,1.5	**Gupta et al.** (1994),(varying)
The maximum number of mosquitoes	M^0	k_0N^0	
Crowding parameter of mosquitoes	x	$(g-\eta)/M^0$	
Reduction factor of transmission from ruminants vaccinated by live vaccines to mosquitoes	δ	0-1, 0.8	(varying)
Reduction factor of transmission in ruminants vaccinated by killed vaccines	σ	0-1, 0.8	(varying)

vaccinated by killed vaccines (V_2) classes. A population of adult female mosquitoes (M) is divided into susceptible (U) and infectious (W). Flow diagrams for both models are shown in Figure 1 and sample parameter values are shown in Table 1. To construct the models, we now lay out the assumptions for each type of vaccine.

2.1 LIVE VACCINES

Host demography. The susceptible class is increased by births at rate $\Lambda_r(S, I, R, V_1)$. We further assume that due to limited resources or human demands and abortions of ruminants from RVFV, Λ_r is described by a logistic function $(b-qN)(S+R)+r_1(b-qN)I+r_2(b-qN)V_1$, where b is a birth rate of ruminants, q is a parameter reflecting the limited number of ruminants in an area, r_1 is a proportion of surviving newborns from infected ruminants (as RVF infection can cause high abortion in pregnant ruminants (**McElroy et al.** (2009))), and r_2 is a proportion of surviving newborns from ruminants vaccinated with live vaccines (as

live vaccines can cause abortion in early-stage pregnant ruminants (**Kamal** (2011))). All ruminant classes decrease due to natural death and slaughter at rate μ. RVF infection causes high mortality in ruminants (**Evans et al.** (2008)) and only some animals recover with life-long immunity (**Barnard** (1979); **Paweska et al.** (2005)). Hence, ruminants die due to RVFV at rate d and recover at rate γ.

Vector demography. We assume that mosquitoes die at rate η and there is no vertical transovarial transmission so that mosquitoes are born disease-free at rate Λ_m, a logistic function $(g-xM)M$, where g is a birth rate of mosquitoes and x is a crowding parameter for mosquitoes. Note that vertical transmission is present in East Africa but not currently present in the Middle East and West Africa (**El-Rahim et al.** (1999); **Martin et al.**) and we are primarily interested in understanding the effects of RVF on ruminant populations and how those effects are influenced by the use of vaccines so that we does not include vertical transmission in our study.

Live vaccines. Although live vaccines induce early and long-term immunity, they may cause viraemia in ruminants and have a potential for virulence reversion so that they are not recommended in non endemic areas or during the breeding season of mosquitoes or during disease outbreaks (**Ikegami and Makino** (2009); **Kamal** (2011)). Susceptible ruminants are vaccinated at rate $\rho_{11}\phi_1$, where $1/\phi_1$ is the time period that ruminants remain susceptible before being vaccinated and only some fraction ρ_{11} of ruminants is actually vaccinated. Vaccinated ruminants leave the vaccination class at rate λ with a probability of ρ_{12} to successfully acquire a life-long immunity, a probability of ρ_{13} that reversion to virulence occurs, and a probability of $1-\rho_{12}-\rho_{13}$ for vaccine failure.

Transmission. Susceptible ruminants become infected at rate βWS, where β is a per capita transmission rate from infectious mosquitoes to susceptible ruminants and it is a function of a per capita biting rate (a) and a probability of successful infection in ruminants (p_r). Susceptible mosquitoes become infected from biting infectious ruminants at rate αUI, where α is a per capita transmission rate from infectious ruminants to susceptible mosquitoes and it is a function of a per capita biting rate (a) and a probability of successful infection in mosquitoes (p_m). Here, we assume that ruminants vaccinated by live vaccines can transmit RVFV to mosquitoes due to viraemia but the transmission is reduced by a factor δ from the rate of transmission from infectious ruminants. If $\delta = 1$, there is no viraemia in vaccinated ruminants and if $\delta = 0$, there is no reduction of viraemia in vaccinated ruminants compared to infectious ruminants.

The changes in abundances of ruminants and mosquitoes over time can be described by a system of ordinary differential equations:

$$\begin{aligned}
\dot{S} &= \Lambda_r(S,I,R,V_1) + (1-\rho_{12}-\rho_{13})\lambda V_1 - \beta WS - \rho_{11}\phi_1 S - \mu S,\\
\dot{I} &= \beta WS + \rho_{13}\lambda V_1 - (\mu + d + \gamma)I,\\
\dot{R} &= \gamma I + \rho_{12}\lambda V_1 - \mu R,\\
\dot{V_1} &= \rho_{11}\phi_1 S - (\mu+\lambda)V_1,\\
\dot{U} &= \Lambda_m(M) - \alpha IU - (1-\delta)\alpha V_1 U - \eta U,\\
\dot{W} &= \alpha IU + (1-\delta)\alpha V_1 U - \eta W.
\end{aligned} \tag{1}$$

KILLED VACCINES

Host demography. As killed vaccines are safe and do not lead to abortions in ruminants (**Ikegami and Makino** (2009); **Kamal** (2011)), we assume that Λ_r is described by a logistic function $(b-qN)(S+R+V_2) + r_1(b-qN)I$.

Vector demography. We use similar assumptions as live vaccines.

Killed vaccines. Although killed vaccines are safer than live vaccines, they may have poor immunogenicity, not inducing long-term immunity and often requiring multiple vaccination doses (**Ikegami and Makino** (2009); **Bird** (2012)). We assume that susceptible ruminants are vaccinated at rate $\rho_{21}\phi_2$, where $1/\phi_2$ is the time period that ruminants remain susceptible before being vaccinated by killed vaccine and only some fraction ρ_{21} of ruminants is actually vaccinated. Vaccinated ruminants leave the vaccination class at rate ν with a probability of ρ_{22} to receive booster vaccines and successfully acquire long-term immunity, and a probability of $1-\rho_{22}$ for individuals to become susceptible again due to vaccine failure or not receiving booster vaccines.

Transmission. Not only susceptible ruminants but also ruminants vaccinated by killed vaccines (that may not induce complete protection against infections due to waning of an effective level of immunity (**Bird** (2012); **Boshra et al.**)) may become infected. However, we assume that infectiousness in the latter group of animals is reduced by a fraction σ, which represents the degree of protection induced by primary vaccination. Hence, susceptible and vaccinated ruminants become infected at rate βWS and $(1-\sigma)\beta WV_2$, respectively. Note that there is full protection against infections by killed vaccines if $\sigma = 1$ and there is no protection if $\sigma = 0$. Unlike live vaccines, killed vaccines with proper inactivation are not likely to cause viraemia in animals (**Bird** (2012)). Hence, we assume that only infectious ruminants can transmit RVFV to mosquitoes at rate αUI.

The assumptions lead to the following system of equations:

$$\begin{aligned}
\dot{S} &= \Lambda_r(S,I,R,V_2) + (1-\rho_{22})\nu V_2 - \beta WS - \rho_{21}\phi_2 S - \mu S,\\
\dot{I} &= \beta WS + (1-\sigma)\beta WV_2 - (\mu + d + \gamma)I,\\
\dot{R} &= \gamma I + \rho_{22}\nu V_2 - \mu R,\\
\dot{V_2} &= \rho_{21}\phi_2 S - (1-\sigma)\beta WV_2 - (\mu+\nu)V_2,\\
\dot{U} &= \Lambda_m(M) - \alpha IU - \eta U,\\
\dot{W} &= \alpha IU - \eta W.
\end{aligned} \tag{2}$$

3 RESULTS

When a vaccination program by is not implemented, the models (2) and (3) are the same. RVFV dies out if $R_0 < 1$ and is endemic if $R_0 > 1$ where

$$R_0 = \frac{\beta\alpha M^0 N^0}{\eta(\mu + d + \gamma)} \tag{3}$$

and R_0 is the basic reproductive number of (1) with $\phi_1 = \rho_{11} = 0$ (see Protocol 1 in Supplementary Material for the derivation of this formula and analysis of the system (1)). From this formula, persistence of RVFV depends on transmission rates between ruminants and mosquitoes, numbers of ruminants and mosquitoes, lifespan of ruminants, RVF-related death rate, and recovery rate. However, when live vaccines are administered, RVFV always persists even when $R_0 < 1$ in the system without vaccination. The persistence of RVFV when live vaccines are used is because some fraction of ruminants vaccinated with live vaccines become infected by reversion to virulence (ρ_{13}). Figure 2A shows that RVFV is endemic when $R_0 > 1$ regardless of whether a vaccination program is implemented. However, when $R_0 < 1$, RVFV dies out when there is no implementation of the vaccination program by live vaccines and is endemic when there is the implementation.

In case killed vaccines are used in an area, RVFV dies out if $R_0^k < 1$ and is endemic if $R_0^k > 1$ where R_0^k is the basic reproductive number of (2) and is given by

$$R_0^k = R_0 \frac{\mu(\mu+\nu) + (1-\sigma)\mu\rho_{21}\phi_2}{(\rho_{21}\rho_{22}\phi_2\nu + \rho_{21}\phi_2\mu + \mu(\mu+\nu))} < R_0. \quad (4)$$

(see Protocol 2 in Supplementary Material for the derivation of this formula and analysis of the system (2)). Differently, apart from parameters that appear in R_0, persistence of RVFV in ruminant and mosquito populations also depends on parameters associated with killed vaccines, vaccination rate, the probability that ruminants are vaccinated, vaccine efficacy, and the probability of receiving a repeated dose of killed vaccine. Consequently, it may be possible to eliminate RVFV by increasing vaccination attempts and vaccine efficacy. When a vaccination program by killed vaccines is not implemented ($\rho_{21} = \rho_{22} = \phi_2 = 0$), R_0^k is equivalent to R_0. In Figure 2B, whether the vaccination program by killed vaccines is or is not implemented, RVFV is endemic when $R_0^k > 1$. However, by increasing vaccination rate so that $R_0^k < 1$, RVFV dies out.

Under the assumption that some ruminants are vaccinated by live or killed vaccines before an outbreak occurs (42% of the ruminant population for instance-this quantity is estimated from the vaccination rate and two months of warning of RVF activities in Table 1), the magnitude of an outbreak in our numerical studies (which we will call the epidemic size through the rest of this work) when live vaccines are used or ruminants vaccinated by live vaccines are introduced in an area is higher than the case of killed vaccines (Figure 2A-B). Note that there is less difference when vaccination is not continued after an introduction of diseased or vaccinated ruminants. Moreover, in Figure 2A-B, it can be clearly noticed that outbreaks in areas where killed vaccines are used occur later than in areas where live vaccines are used. We further investigate the duration from an introduction of diseased ruminants to time that an RVF outbreak peaks (see Protocol 3 in Supplementary Material). We found that this duration is shorter in areas where live vaccines are administered as compared to areas where killed vaccines are administered and it is shortened by increasing probability that ruminants are vaccinated by live vaccines and decreasing efficacy of live vaccines (the probability of acquiring immunity from live vaccines has small effect). On the other hand, the duration is lengthened by increasing probability that ruminants are vaccinated by killed vaccines and efficacy of killed vaccines that prevents RFV infection or the challenge by virulent strains of RVFV (the probability of receiving a booster dose of killed vaccines has small effect in the first outbreak). Hence, outbreaks may peak in areas where live vaccines with poor efficacy are heavily used before they peak in areas that killed vaccines are administered.

Albeit the basic reproductive number is a very useful measure to determine whether diseases can spread through ruminant and mosquito populations, and severity of the disease spread as measured by the magnitude of outbreaks and the endemic number are increasing functions of it (**Brauer et al.** (2008)), there are also many factors that influence severity of the disease spread, for instance the number of vaccinated ruminants at the beginning of an outbreak and delay of launching a vaccination program for RVF transmission. Figure 2C shows that the epidemic size is reduced by increasing the beginning number of vaccinated ruminants by live or killed vaccines. Although it cannot be easily seen in Figure 2C, by studying slopes that represent the changes of epidemic sizes according to the changes of numbers of ruminants vaccinated by live and killed vaccines, we find that epidemic sizes are reduced by the increased number of vaccinated ruminants. Moreover, the reduction of epidemic sizes occurs slowly when a small number of ruminants are vaccinated by live vaccines and then increases quickly when numbers of vaccinated ruminants become bigger, while it occurs quickly when a small number of ruminants are vaccinated by killed vaccines and moderately when larger numbers of ruminants are vaccinated. As ruminants vaccinated by live vaccines may transmit RVFV to mosquitoes, we investigate whether an outbreak occurs when ruminants are vaccinated by live vaccines as preparedness or are introduced in areas with $R_0 < 1$ and without further vaccine administration (Hence, RVFV does not persist). Figure 2D shows that an outbreak occurs and has more significant impacts when numbers of vaccinated ruminants increase. However, when numbers of ruminants vaccinated by live vaccines are approximately more than

a half of the ruminant population in our study, the epidemic size starts to decrease. In Figure 2E, when there is delay in launching a vaccination program by killed vaccines, the longer the delay the higher the epidemic size, and the epidemic reaches the same size as when there is no vaccination if the delay is sufficiently long (approximately 3 months). However, the delay has less effect when it is small but has more effect when it reaches certain periods (approximately 50 days in Figure 2E) for live vaccines.

Next we investigate the impacts of vaccination attempts $(\rho_{11}, \rho_{21}, \rho_{22})$ and efficacy (ρ_{12}) on the epidemic size and the endemic number (as measured by the number of infectious ruminants at the disease-present steady state). Figure 3A shows that the probability that ruminants are vaccinated by live vaccines has less effect on the epidemic size than probability of successfully acquiring immunity of ruminants. However, both have less effect when there are no ruminants vaccinated by live vaccines at the beginning of an outbreak (Protocol S3). When some of the ruminants are vaccinated by killed vaccines before an outbreak starts, both the probability that ruminants are vaccinated by killed vaccines and the probability that ruminants successfully receive repeated doses of killed vaccines influence the epidemic size, but if none of the ruminants are vaccinated before the beginning of the outbreak, the probability that ruminants are vaccinated by killed vaccines has more impact (Figure 3B and Protocol S3). As shown in Figure 3C-D, all of those quantities have certain effects on the prevalence of RVFV in ruminants. By further investigating them with different vaccine efficacy (relating to ρ_{13}, δ, and σ), the results are similar and the better the vaccine efficacy, the smaller the outbreak and the endemic number. Note that additional results not included in Figure 3 can be found in Protocol S3.

Because of the periodic or sporadic nature of outbreaks and economically limited access to vaccine, continuous vaccination efforts on RVFV do not take place in many endemic areas. Figure 4A-B show the number of infectious ruminants in correspondence with the administration of live or killed vaccines for two years before discontinuing it for the next two years. From the results, the termination of continuous vaccination efforts may cause small outbreaks in both live and killed vaccine cases, and although the first outbreak is more serious when live vaccines are used, it is more likely that subsequent outbreaks are smaller than when killed vaccines are used. Moreover, killed vaccines have more impact on reducing the severity of outbreaks when periods of using and discontinuing vaccines are lengthened while the periods have less effect when live vaccines are administered (from two years to five and ten years)(Figure 4C-D).

Ruminants are often recruited to replace dead or consumed animals in many areas. We investigate introduction of new susceptible ruminants into the ruminant population at the beginning of every year or every three years (these periods can be adjusted to account for the banning of imported animals by government after an outbreak occurs) by introducing pulses of animal recruitment into $\dot{S}$ to represent an introduction of susceptible animals at particular points as

$$\sum_{n=1}^{\infty}(N^0 - N(t))\delta(t - nT),$$

where T is a fixed period of introduction, $n = 1, 2, 3, \ldots$, and δ is a Dirac delta function such that $\delta(t - nT) = 1$ when $t = nT$ and $\delta(t - nT) = 0$ elsewhere. Figure 5A-B suggest that small outbreaks occur in areas that ruminants are recruited. Their frequency is reduced by the extended period of animal recruitment and their severity is decreased by (live or killed) vaccine administration. Let us assume that some ruminants in the endemic areas are consumed at the end of every year for a religious feast and new ruminants are recruited to replace them and other dead ruminants afterward. RVF outbreaks are more likely to occur when the percentage of recruited ruminants with acquired immunity to RVFV is reduced and more ruminants are consumed during the feast (Figure 5C-D). The percentage of recruited ruminants with acquired immunity has more impacts on both frequency and severity of outbreaks than the number of consumed ruminants. Moreover, outbreaks are more likely to happen when live vaccines are used in endemic areas (spiny peaks for live vaccines and unpointed peaks for killed vaccines). Note that in Figure 5C-D, we assume that 20% or 50% of ruminants are eaten during a feast in each year; more than 80% or 50% of recruited ruminants are immune to RVFV (ruminants are vaccinated and quarantined until they successfully acquire immunity before animal recruitment); less than 1% of recruited ruminants

are infectious; and other recruited ruminants are either susceptible or vaccinated. The probability that ruminants are in each disease status is chosen randomly in our simulation study and only a lower bound of the percentage of immune ruminants in recruited ruminants and an upper bound of the percentage of infectious ruminants in recruited ruminants are given. Hence, for instance, $-0.2\sum_{n=1}^{\infty} R\delta(t-n(T-\varepsilon))+p_{\geq 0.8}^{\text{random}}\sum_{n=1}^{\infty}(N^0-N(t))\delta(t-nT)$ where $\varepsilon\to 0$ (20% of immune ruminants are consumed and more than 80% of recruited ruminants are immune) is added into $\dot{R}$.

It has been suggested that RVF outbreaks are often associated with high numbers of mosquitoes. Figure 6A shows that the mosquito:ruminant ratio has drastic effects (as compared to the mosquito lifespan) on the severity of an outbreak such that a higher mosquito:ruminant ratio leads to a larger epidemic size of the outbreak. To consider the effect of seasonal abundance of mosquitoes, we assume that the mosquito:ruminant ratio fluctuates over time as a sinusoidal function such that the mosquito:ruminant ratio is highest at the middle of the wet season and lowest at the middle of the dry season as follows:

$$k = k_1(1 - k_2\cos 2\pi t),$$

with $k_2 = (k_{\max}/k_{\min}-1)/(k_{\max}/k_{\min}+1)$, $k_1 = k_{\max}/(1+k_2)$, and $M = kN^0$ (**Altizer et al.** (2006); **Childs and Boots** (2010)) with k ranging from 0.2 to 2 in our numerical study. Hence, when abundance of mosquitoes is seasonal, after the first outbreak, the number of infectious ruminants peaks slightly after the middle of each year according to the seasonal mosquito abundance (Figure 6B). By assuming that 20% of ruminants are consumed at the end of each year and that to replace dead or consumed ruminants ruminants are recruited with at least 50% of them immune to RVFV (vaccinated and successfully acquiring immunity) and less than 1% of them infectious, Figure 6C shows that recruiting ruminants during the high activity instead of low activity of mosquitoes may cause outbreaks and serious outbreaks are more likely to occur in areas where live vaccines are administered and larger numbers of ruminants with no immunity are recruited. In Figure 6D, small outbreaks may occur when ruminants are vaccinated by live vaccines during seasons of high activity of mosquitoes and their severity increases if the mosquito:ruminant ratio increases and more vaccinated ruminants have viraemia from live vaccines. However, when seasons of high activity of mosquitoes are longer than seasons of low activity of mosquitoes, the severity of those outbreaks increases and administration of live vaccines is recommended even during seasons of high activity of mosquitoes. This result is not surprising because routine and continuous vaccination is probably more effective to control RVFV.

4 DISCUSSION

We have developed two modeling frameworks to investigate the transmission dynamics of RVFV among ruminants via mosquitoes and the impact of using live or killed vaccines to control the spread of RVFV. Advantages and disadvantages of live and killed vaccines were incorporated and several factors that may influence severity of outbreaks, the prevalence of RVFV, the recurrence of RVF outbreaks, and the virus introduction such as delay in vaccination, efficacy of vaccines, recruitment of animals, quarantine strategies, the abundance of mosquitoes, and vaccination strategies were considered in our study.

It has been observed in many endemic areas that the prevalence of RVFV remains at a very low level after an outbreak: 1-3% of livestock being infected with RVFV in certain areas of Africa during non epizootic period and as low as 0.1% in Yemen (**Davies et al.** (1992); **Rostal et al.** (2010); **Abdo-Salem et al.** (2011b)). Similarly, our models predicted that RVFV remains endemic at a very low level after an outbreak as the high number of infected ruminants become immune to RVFV. The basic reproductive number (R_0) is an important quantity in epidemiology and has played a crucial role in disease control. It potentially determines whether a disease can spread through a population and is defined as the expected number of secondary infections resulting from an introduction of a single infected individual into a completely susceptible population; the number of infected individuals increases if $R_0 > 1$ and decreases if $R_0 < 1$ (**Brauer et al.** (2008)). It also helps determine persistence and severity of the disease spread as the

epidemic size and the endemic number of infected individuals are increasing functions of it. To eliminate the parasite or reduce its severity and burden, sustained disease control needs to be implemented to ensure that R_0 is less than one or as small as possible. Our results demonstrate that the basic reproductive number of RVFV without vaccination generally depends on transmission rates between ruminants and mosquitoes, numbers of ruminants and mosquitoes, lifespan of ruminants, RVF-related death rate, and recovery rate and is given by

$$R_0 = \frac{\beta\alpha M^0 N^0}{\eta(\mu + d + \gamma)}.$$

In case live vaccines are constantly administered in prevention strategies, RVFV persists despite $R_0 < 1$ (due to the possibility that ruminants vaccinated by live vaccines may transmit RVFV to mosquitoes and reversion to virulence of live vaccines in ruminants may occur) and there is no particular formula for the basic reproductive number that gives information of live vaccines. Contrarily, the basic reproductive number when killed vaccines are used as a preventive tool (R_0^k) can be calculated and is proportional to R_0 ($R_0^k < R_0$) and associated with the killed vaccine parameters. This suggests that it may be possible to eliminate RVFV by increasing vaccination attempt and killed-vaccine efficacy so that $R_0^k < 1$. We further found that the magnitude of an outbreak or the epidemic size when live vaccines are used in prevention strategies is more likely to be higher than killed vaccines under the same vaccination rate and probability of protection against infection due to the possibility that ruminants vaccinated by live vaccines may transmit RVFV to mosquitoes and reversion to virulence may occur. Interestingly, for similar reasons, we also found that an outbreak peaks in areas where killed vaccines are used after it does in areas where live vaccines are used and the number of vaccinated ruminants and vaccine efficacy play an important role in the timing. In addition, the duration from an introduction of diseased ruminants to the time that an RVF outbreak peaks is shortened by increasing the probability that ruminants are vaccinated by live vaccines and decreasing the probability that live vaccines may cause viremia, but is lengthened by increasing probability that ruminants are vaccinated by killed vaccines and efficacy of killed vaccines to prevent RFV infection or the challenge by virulent strains of RVFV. Knowing the period over which the outbreak extends could be useful in designing the most effective mosquito control strategies. So far our results support several studies that suggest the use of killed vaccines in non-endemic areas and attribute the persistence of RVFV in some cases to the use of live vaccines that may contaminate the environment and cause transmission of RVFV from vaccinated animals to mosquitoes (**Kamal** (2009, 2011); **von Teichman et al.** (2011)).

Although the basic reproductive number provides important information for the spread of RVFV, it only gives partial information as the severity of an outbreak (or the epidemic size in our study) and the endemic number (or the number of infectious ruminants at the disease-present steady state) are influenced by several factors. The number of vaccinated ruminants is one of those factors that plays a crucial role in reducing the number of infected ruminants during epizootic and enzootic cycles of RVFV. Remote sensing satellite data of sea-surface temperatures, rainfall, and intensity of green vegetation have been used to investigate and predict mosquito and RVF activities (**Linthicum et al.** (1999)). Prediction from such information could provide a 2 to 6 week period of warning and such an approach proved to be effective in East Africa (**Anyamba et al.** (2009)). Our results show that the epidemic size is reduced when more ruminants are vaccinated before an outbreak occurs and hence better advanced warning of RVF outbreaks may aid preparedness and provide sufficient time to vaccinate ruminants, raise the herd immunity, and consequently reduce the epidemic size. Moreover, we found that the reduction of epidemic sizes occurs slowly when a few of ruminants are vaccinated by live vaccines but then the epidemic size reduces quickly when numbers of vaccinated ruminants become larger, while the reduction occurs quickly when a few of ruminants are vaccinated by killed vaccines but only moderately when more ruminants are vaccinated.

One of the surprising results obtained in our study is that an outbreak may occur in areas where ruminants are vaccinated by live vaccines for preparedness or are introduced in areas with $R_0 < 1$ and there is no further vaccine administration of live vaccines. The reason is that vaccinated ruminants may

transmit RVFV to mosquitoes, and intermediate numbers of vaccinated ruminants may lead to a more serious outbreak than when a small or large number of ruminants are vaccinated. This finding supports several studies that suggest the use of killed vaccines in non-endemic areas (**Kamal** (2009, 2011); **von Teichman et al.** (2011)). The early detection of RVFV activities is important for effective control to minimize outbreak consequences. However, it is possible that several weeks or months occur between the presumptive start of an outbreak and its initial detection by public health and veterinary authorities due to delay in diagnosis, reporting of infection, and limited vaccination resources (**McElroy et al.** (2009); **Bird** (2012)). Our results demonstrate that delay in launching a vaccination program may lead to more serious outbreaks and that outbreaks can reach the same epidemic size comparable to no vaccination at all when the delay is long enough. A good example which supports this finding is a major 2006-2007 outbreak in East Africa in which the public health community was alerted several months before the first confirmed human cases were reported but few preventive steps were taken before laboratory confirmation, causing a delay of almost 8 weeks in the administration of vaccine, with a substantial loss of humans and livestock (**Anyamba et al.** (2009); **Bird** (2012)). In addition, our results suggest that the delay has effect on the epidemic size even though it is small for killed vaccines. In the case of live vaccines, delay has less effect when it is small but more effects when it becomes larger. Hence, according to our findings, RVF outbreaks in non-endemic areas can be very severe as there is presumably delay in vaccine implementation due to unpreparedness.

Vaccine efficacy and vaccination strategies are important determinants of effective control; imperfect vaccines that give incomplete protection and the loss of vaccine-induced immunity, for instance, may not help prevent severe outbreaks and their resurgence efficiently (**Keeling and Rohani** (2007)). Our results suggest that inefficient vaccines and vaccination strategies can lead to the higher epidemic size and the higher endemic number as compared to efficient vaccines and vaccination strategies. Furthermore, the percentage of ruminants vaccinated by live vaccines has less impact on the epidemic size than the percentage of ruminants that successfully acquire long-term immunity, but both have less impact when ruminants are not vaccinated before an outbreak. For killed vaccines, both the percentage of vaccinated ruminants and the percentage of ruminants receiving vaccine boosters have impact on the epidemic size, but the former has more impact when none of ruminants are vaccinated before an outbreak starts. All of these factors have significant impact on the endemic number so that the better the efficacy, the lower the endemic number. Other efficacy factors (the probability of reversion to virulence, the reduction factor of transmission from ruminants vaccinated by live vaccines to mosquitoes, and the reduction factor of infection in ruminants vaccinated by killed vaccines) also have certain influence on the epidemic size and the endemic number. Our results underline how important vaccine efficacy and vaccination strategies are for controlling RVFV and highlight the need of effective vaccines and vaccination strategies.

Vaccination is an effective means to control the spread of diseases and prevent disease-related losses but has proved to be challenging for RVF due to the sporadic and explosive nature of the outbreaks and economically limited access to vaccine (**McElroy et al.** (2009)). Sustaining vaccination programs in ruminants during enzootic cycles for this disease that appears infrequently and vaccinating massive numbers of ruminants during ongoing epizootics has proved difficult (**McElroy et al.** (2009); **Rusnak et al.** (2011)). We investigated the consequences of this periodic-like vaccine administration and found that the lack of continuous vaccination efforts may cause small outbreaks for both live and killed vaccine cases in endemic areas. Moreover, in the long term, subsequent outbreaks are smaller when live vaccines are used as compared to killed vaccines. The use of killed vaccines is better at reducing the severity of outbreaks when periods of using and discontinuing vaccines are lengthened as compared to when such periods are shortened while the difference in usage durations have less effects to live vaccines.

Recruitment of ruminants into an area for consumption or for maintenance of the size of animal herds may involve the introduction of a massive number of susceptible ruminants. We investigated the impact of the presence of susceptible ruminants on epizootic and enzootic cycles and found that small outbreaks may occur in endemic areas when susceptible ruminants are recruited. Moreover, the frequency of outbreaks is reduced by the extended period of animal recruitment and their severity is decreased by live or killed vaccine administration. This finding corresponds to some studies suggesting that cattle of owners who

purchased ruminants to replace their herds following outbreaks were significantly more antibody-positive than others (**Chevalier et al.** (2011)), and supports a control measure that suggest a ban of animal importation after an outbreak (**Al-Afaleq and Hussein** (2011); **Abdo-Salem et al.** (2011b)). In many areas, ruminants are imported and consumed for religious festivals (or are imported to replace dead or consumed ruminants as we previously mentioned) (**Al-Afaleq and Hussein** (2011); **Abdo-Salem et al.** (2011b); **Thiongane et al.** (1997)). For international trade of ruminants, surveillance and certification systems are required for exported countries in order to minimize the risk of the spread or introduction of important diseases; for example, Ethiopia has collection and quarantine points where ruminants are gathered, fed, treated, vaccinated, and kept for approximately 20 to 30 days (**Abdo-Salem et al.** (2011b)). The importation of ruminants may involve a number of ruminants with different disease status. Hence, we explored how different percentages of immune (vaccinated and quarantined) and susceptible (quarantined but not vaccinated) ruminants and different percentages of animal consumption in the areas in which live or killed vaccines are administered influence RVF activities. Our results demonstrate that RVF outbreaks are more likely to occur when the percentage of recruited ruminants with acquired immunity to RVFV is reduced and more ruminants are consumed. More interestingly, the percentage of recruited ruminants with acquired immunity has a greater impact on both frequency and severity of outbreaks than the number of consumed ruminants, and, moreover, outbreaks are more like to happen when live vaccines are used. These findings may provide important insight for designing control strategies.

It has been observed in many studies that RVF outbreaks are closely linked to heavy rainfall and high numbers of mosquitoes (**Linthicum et al.** (1999); **Anyamba et al.** (2009); **Bird** (2012)). Furthermore, RVF virus activity occurs annually and is associated with seasonal rains during non-epidemic periods (**Davies et al.** (1992)). Our results also show that a high number of mosquitoes may increase the epidemic size of an outbreak, the number of mosquitoes has more impact on the epidemic size than the mosquito lifespan, and RVF cases fluctuate according to seasonal abundance of mosquitoes (with a small delay in an outbreak peak and a peak of mosquito numbers). One of the interesting results related to mosquito activities and obtained in our study is that recruiting ruminants during periods of the high activity versus low activity of mosquitoes may cause outbreaks and serious outbreaks are more likely to occur in areas in which live vaccines are administered and many ruminants with no immunity are recruited. This finding may generally suggest that implementing stringent control measures in imported ruminants during a mosquito season may help reduce the epizootic risk. It may also link to some studies suggesting the emergence of RVF in Yemen in 2000 as the confluence of environmental conditions favorable to mosquitoes and high densities of imported ruminants for a religious feast (**Abdo-Salem et al.** (2011a)). Typically, it is recommended and included in the live vaccine description that ruminants should not be vaccinated during breeding season of mosquitoes (**Kamal** (2011)). Our results suggest that small outbreaks may occur when ruminants are vaccinated by live vaccines during a period of high abundance of mosquitoes and the severity of an outbreak increases as the mosquito:ruminant ratio increases and more vaccinated ruminants have viraemia from live vaccines. However, when seasons of high activity of mosquitoes are longer than seasons of low activity of mosquitoes, severity of those outbreaks increases and administration of live vaccines is recommended even during seasons of high activity of mosquitoes.

Together with several factors that may influence RVF activities, our models that capture advantages and disadvantages of live versus killed vaccine allow us to investigate the impact of vaccination by live and killed vaccines on the RVFV dynamics during epizootic and enzootic periods that (to our knowledge) have not been addressed in any previous modeling studies. Although a number of simplifying assumptions are made (for example, difficulty of administration and storing and prices of vaccines were not taken into account) and there is limited information on certain model parameters (for example, the percentage of ruminants that receive booster vaccines was set high while it may be lower in real events), several findings in our study correspond to previous empirical studies while others make predictions that can be further investigated. All in all, we believe that this particular study may be useful in understanding the dynamics of RVFV among ruminants in areas in which vaccination is implemented, identifying the key variables, helping indicate advantages and disadvantages of live versus killed vaccines, underlining the need of effective vaccines, and providing important insights for designing effective control strategies.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Health (NIH) grant R01GM093345.

REFERENCES

Abdo-Salem, S., Tran, A., Grosbois, V., Gebier, G., Al-Qadasi, M., Saeed, K., et al. (2011a), Can environmental and socioeconomic factors explain the recent emergence of Rift Valley fever in Yemen, 2000-2001?, *Vector-borne Zoonot.*, 11, 773–779

Abdo-Salem, S., Waret-Szkuta, A., Roger, F., Olive, M., Saeed, K., and Chevaller, V. (2011b), Risk assessment of the introduction of Rift Valley fever from the Horn of Africa to Yemen via legal trade of small ruminants, *Trop. Anim. Health Prod.*, 43, 471–480

Al-Afaleq, A. I. and Hussein, M. F. (2011), The status of Rift Valley fever in animals in Saudi Arabia: a mini review, *Vector-borne Zoonot.*, 11, 1513–1520

Altizer, S., Dobson, A., Hosseini, P., Hudson, P., Pascual, M., and Rohani, P. (2006), Seasonality and the dynamics of infectious diseases, *Ecol. Lett.*, 9, 467–487

Andriamandimby, S. F., Randrianarivo-Solofoniaina, A. E., Jeanmaire, E. M., Ravololomanana, L., Razafimanantsoa, L. T., Rakotojoelinandrasana, T., et al. (2010), Rift Valley fever during rainy seasons, Madagascar, 2008 and 2009, *Emerg. Infect. Dis.*, 16, 963–970

Anyamba, A., Chretien, J., Small, J., Tucker, C. J., Formenty, P. B., Richardson, J. H., et al. (2009), Prediction of a Rift Valley fever outbreak, *Proc. Natl. Acad. Sci. USA*, 106, 955–959

Barnard, B. J. H. (1979), Rift Valley fever vaccine-antibody and immune response in cattle to a live and an inactivated vaccine, *J. S. Afr. Vet. Assoc.*, 50, 155–157

Bicout, D. J. and Sabatier, P. (2004), Mapping Rift Valley fever vectors and prevalence using rainfall variations, *Vector-borne Zoonot.*, 4, 33–42

Bird, B. H. (2012), Breaking the chain: Rift Valley fever virus control via livestock vaccination, *Curr. Opin. Virol.*, 2, 1–9

Boshra, H., Lorenzo, G., Busquets, N., and Brun, A. (????), Rift Valley fever: recent insights into pathogenesis and prevention, *J. Virol.*, 85, 6098–6105

Brauer, F., van den Driessche, P., and (Eds.), J. W. (2008), Mathematical Epidemiology (Springer, Berlin, Heidelberg)

Chamchod, F., Cantrell, R. S., Cosner, C., Hassan, A. N., Beier, J. C., and Ruan, S. (2014), A modeling approach to investigate epizootic outbreaks and enzootic maintenance of Rift Valley fever virus, *Bull. Math. Biol.*, 76, 2052–2072

Chevalier, V., Rakotondrafara, T., Jourdan, M., Heraud, J. M., Andriamanivo, H. R., Durand, B., et al. (2011), An unexpected recurrent transmission of Rift Valley fever virus in cattle in a temparate and mountainous area of Madagascar, *PLoS Neglect. Trop. D.*, 5, e1423

Childs, D. Z. and Boots, M. (2010), The interaction of seasonal forcing and immunity and the resonance dynamics of malaria, *J. R. Soc. Interface*, 7, 309–319

Davies, F. G., Kilelu, E., Linthicum, K. J., and Pegram, R. G. (1992), Patterns of Rift Valley fever virus, *Epidemiolo. Infect.*, 108, 185–191

Dye, C. (1984), Models for the population dynamics of the yellow fever mosquito, *Aedes aegypti*, *J. Anim. Ecol.*, 53, 247–268

El-Rahim, I. H. A. A., El-Hakim, U. A., and Hussein, M. (1999), An epizootic of Rift Valley fever in egypt in 1997, *Rev. sci. tech. Off. int. Epiz.*, 18, 741–748

Evans, A., Gakuya, F., Paweska, J. T., Rostal, M., Akoolo, L., and et al. (2008), Prevalence of antibodies against Rift Valley fever virus in Kenyan wildlife, *Epidemiol. Infect.*, 136, 1261–1269

Favier, C., Chalvet-Monfray, K., Sabatier, P., Lancelot, R., Fontenille, D., and Dubois, M. A. (2006), Rift Valley fever in West Africa: the role of space in endemicity, *Trop. Med. Int. Health*, 11, 1878–1888

Fontenille, D., Traore-Lamizana, M., Diallo, M., Thonnon, J., Digoutte, J. P., and Zeller, H. G. (1998), New vectors of rift valley fever in West Africa, *Emerg. Infect. Dis.*, 4, 289–293

Gaff, H., Hartley, D. M., and Leahy, N. P. (2007), An epidemiological model of Rift Valley fever, *Electron. J. Differ. Equ.*, 2007, 115, 1–12

Gao, D., Cosner, C., Cantrell, R. S., Beier, J. C., and Ruan, S. (2013), Modeling the spatial spread of Rift Valley fever in egypt, *Bull. Math. Biol.*, 75, 523–542

Gupta, S., Swinton, J., and Anderson, R. M. (1994), Theoretical studies of the effects of heterogeneity in the parasite population on the transmission dynamics of malaria, *Proc. R. Soc. Lond. B*, 256, 231–238

Hancock, P. A., Thomas, M. B., and Godfray, H. C. J. (2009), An age-structured model to evaluate the potential of novel malaria-control interventions: a case study of fungal biopesticide sprays, *P. Roy. Soc. Lond. B. Bio*, 276, 71–80

Hollidge, B. S., Gonzalez-Scarano, F., and Soldan, S. S. (2010), Arboviral encephalitides: transmission, emergence, and pathogenesis, *J. Neuroimmune. Pharm.*, 5, 428–442

Ikegami, T. and Makino, S. (2009), Rift Valley fever vaccines, *Vaccine*, 27, D69–D72

Kamal, S. A. (2009), Pathological studies on postvaccinal reactions of Rift Valley fever in goats, *Virol. J.*, 6, 94

Kamal, S. A. (2011), Observations on rift valley fever virus and vaccines in Egypt, *Virol. J.*, 8, 532

Keeling, M. J. and Rohani, P. (2007), Modeling Infectious Diseases in Humans and Animals (Princeton University Press, Princeton)

LaBeaud, D. (2010), Towards a safe, effective vaccine for Rift Valley fever virus, *Future Virol.*, 5, 675–678

Linthicum, K. J., Anyamba, A., Tucker, C. J., Kelley, P. W., Myers, M. F., and Peters, C. J. (1999), Climate and satellite indicators to forecast Rift Valley fever epidemics in Kenya, *Science*, 285, 397–400

Linthicum, K. J., Davies, F. G., Kairo, A., and Bailey, C. L. (1985), Rift Valley fever virus (family Bunyaviridae, genus *Phlebovirus*, *J. Hyg (Lond)*, 95, 197–209

Majok, A. A., Zessin, K. H., Baumann, M. P. O., and Farver, T. B. (1991), Analyses of baseline survey data on rinderpest in Bahr el Ghazal Province, with proposal of an improved vaccination strategy against rinderpest for southern Sudan, *Trop. Anim. Health Prod.*, 23, 186–196

Martin, V., Chevalier, V., Ceccato, P., Anyamba, A., Simone, L. D., Lubroth, J., et al. (????), The impact of climate change on the epidemiology and control of Rift Valley fever, *Rev. Sci. tech. Off. int. Epiz.*

McElroy, A. K., Albarino, C. G., and Nichol, S. T. (2009), Development of a RVFV ELISA that can distinguish infected from vaccinated animals, *Virol. J.*, 6, 125

Métras, R., Collins, L. M., White, R. G., Alonso, S., Chevalier, V., Thuranira-McKeever, C., et al. (2011), Rift Valley fever epidemiology, surveillance, and control: what have models contributed?, *Vector-Borne. Zoonot.*, 11, 761–771

Mpeshe, S. C., Haario, H., and Tchuenche, J. M. (2011), A mathematical model of Rift Valley fever with human host, *Acta Biotheor*, 59, 231–250

Munyua, P., Murithi, R. M., Wainwright, S., Githinji, J., Highttwoer, A., Mutonga, D., et al. (2010), Rift Valley fever outbreak in livestock in Kenya, 2006-2007, *Am. J. Trop. Med. Hyg.*, 83, 58–64

Näslund, J., Lagerqvist, N., Habjan, M., Lundkvist, A., Evander, M., Ahlm, C., et al. (2009), Vaccination with virus-like particles protects mice from lethal infection of Rift Valley fever virus, *Virology*, 385, 409–415

Nderitu, L., Lee, J. S., Omolo, J., Omulo, S., ÓGuinn, M. L., Hightower, A., et al. (2011), Sequential Rift Valley fever outbreaks in Eastern Africa caused by multiple lineages of the virus, *J. Infect. Dis.*, 203, 655–665

Paweska, J. T., Mortimer, E., Leman, P. A., and Swanepoel, R. (2005), An inhibition enzyme-linked immunosorbent assay for the detection of antibody to Rift Valley virus in humans, domestic and wild ruminants, *J. Virol. Methods*, 127, 10–18

Pepin, M., Bouloy, M., Bird, B. H., Kemp, A., and Paweska, J. (2010), Rift valley fever virus (*Bunyaviridae: Phlebovirus*): an update on pathogenesis, molecular epidemiology, vectors, diagonostics and prevention, *Vet. Res.*, 41, 61

Reiskind, M. H., Westbrook, C. J., and Lounibos, L. P. (1987), Exposure to Chikungunya virus and adult longevity in *Aedes aegypti* (l.) and *Aedes albopictus* (skuse), *J. Vector. Ecol.*, 37, 640–647

592 Rostal, M. K., Evans, A. L., Sang, R., Gikundi, S., Wakhule, L., Munyua, P., et al. (2010), Identification
593 of potential vectors and detection of antibodies against Rift Valley fever virus in livestock during
594 interepizootic periods, *Am. J. Vet. Res.*, 71, 522–526
595 Rusnak, J. M., Gibbs, P., Boudreau, E., Clizbe, D. P., and Pittman, P. (2011), Immunogenicity and safety
596 of an inactivated Rift Valley fever vaccine in a 19-year study, *Vaccine*, 29, 3222–3229
597 Smith, D. R., Steele, K. E., Shamblin, J., Honko, A., Johnson, J., Reed, C., et al. (2010), The pathogenesis
598 of Rift Valley fever virus in the mouse model, *Virology*, 407, 256–267
599 Smithburn, K. C. (1949), The neurotropic adaptation of the virus and the experimental use of this modified
600 virus as a vaccine, *Br. J. Exp. Pathol.*, 30, 1–16
601 Tesh, R. B., Arroya, J., A. P. A. Travassos da Rosa, H. G., Xiao, S., and Monath, T. P. (2002), Efficacy of
602 killed virus vaccine, live attenuated chimeric virus vaccine, and passive immunization for prevention of
603 West Nile virus encephalitis in hamster model, *Emerg. Infect. Dis.*, 8, 1392–1397
604 Thiongane, Y., Gonzalez, J. P., Fati, A., and Akakpo, J. A. (1997), Changes in Rift Valley fever
605 neutralizing antibody prevalence among small domestic ruminants following the 1987 outbreak in the
606 Senegal River basin, *Res. Virol.*, 142, 67–70
607 Turell, M. J., Linthicum, K. J., Patrican, L. A., Davies, F. G., Kairo, A., and Bailey, C. I. (2008), Vector
608 competence of selected African mosquito (diptera: Culicidae) species for Rift Valley fever virus, *J.*
609 *Med. Entomol.*, 45, 102–108
610 von Teichman, B., Engelbrecht, A., Zulu, G., Dungu, B., Pardini, A., and Bouloy, M. (2011), Safety and
611 efficacy of Rift Valley fever Smithburn and Clone 13 vaccines in calves, *Vaccine*, 29, 5771–5777
612 Wolrld Health Organization (1982), Rift Valley fever: an emerging human and animal problem, *WHO*
613 *Offset Publ.*, 63, 1–69
614 Xiao, Y., Beier, J. C., Cantrell, R. S., Cosner, C., DeAngelis, D. L., and Ruan, S. (2015), Modelling the
615 effects of seasonality and socioeconomic impact on the transmission of Rift Valley fever virus, *PLOS*
616 *Neg. Trop. Dis.*, e3388
617 Xue, L., Scott, H. M., Cohnstaedt, L. W., and Scoglio, C. (2012), A network-based meta-population
618 approach to model Rift Valley fever epidemics, *J. Theor. Biol.*, 306, 129–144

FIGURES

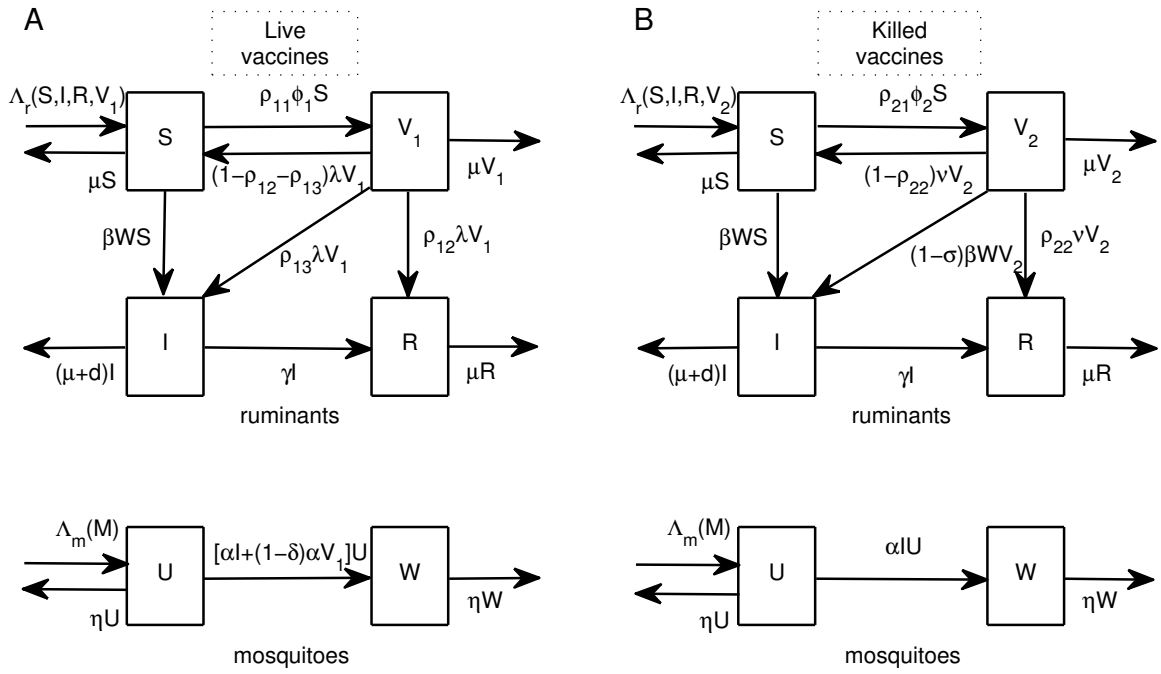

Figure 1. Flow diagrams. Flow diagrams for modeling RVFV transmission between ruminants and mosquitoes for live and killed vaccines are shown in (A) and (B), respectively. Ruminants are divided into four classes: susceptible (S), infectious (I), recovered (R), and vaccinated by live vaccines (V_1) or killed vaccines (V_2). Mosquitoes are divided into two classes: susceptible (U) and infectious (W).

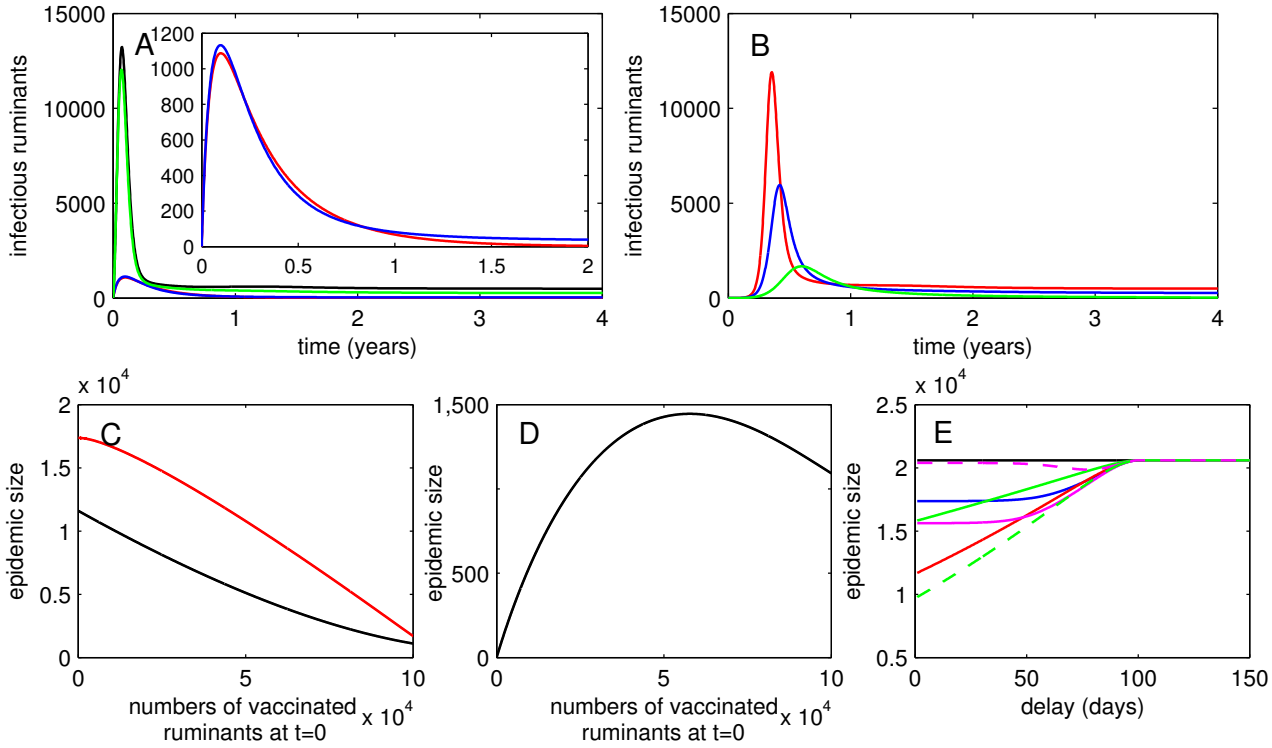

Figure 2. Live and killed vaccines. Infectious numbers of ruminants over time in the case of live vaccines are shown in (A) (black trace = with no vaccination and $R_0 > 1$, green trace = with vaccination and $R_0 > 1$, blue trace = with vaccination and $R_0 < 1$, red trace = with no vaccination and $R_0 < 1$). Comparable information in the case of killed vaccines is shown in (B) (red trace = with no vaccination and $R_0^k > 1$, blue trace = with vaccination and $R_0^k > 1$, green trace = with vaccination and $R_0^k < 1$). (C) shows that the epidemic size of an outbreak decreases when the number of vaccinated ruminants at $t = 0$ increases and $R_0 > 1$ for both live and killed vaccines (red trace = live vaccines, black trace = killed vaccines). The epidemic size of an outbreak when the number of vaccinated ruminants at $t = 0$ varies and $R_0 < 1$ for live vaccines is shown in (D). (E) shows the epidemic size of an outbreak corresponding to the delay in vaccination after an infectious ruminant is introduced for live and killed vaccines (red trace: $\rho_{11} = 0.8$, $\rho_{12} = 0.9$, $\rho_{13} = 0.05$, $\delta = 0.8$, magenta trace: $\rho_{11} = 0.8$, $\rho_{12} = 1$, $\rho_{13} = 0$, $\delta = 0.9$, blue trace: $\rho_{21} = 0.8$, $\rho_{22} = 0.8$, $\sigma = 0.8$, green trace: $\rho_{21} = 0.8$, $\rho_{22} = 1$, $\sigma = 0.9$).

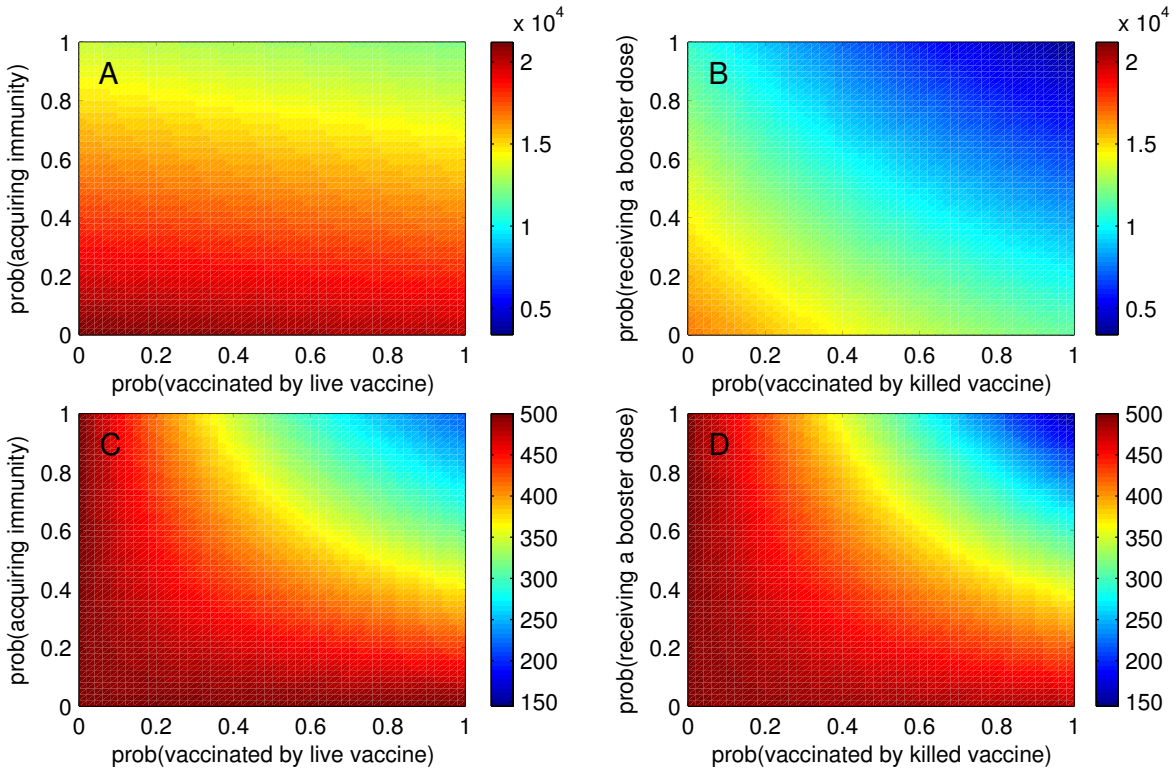

Figure 3. Epidemic size and endemic numbers. (A) The epidemic size of an outbreak for live vaccines when the probability that ruminants are vaccinated (ρ_{11}) and the probability that they acquire immunity (ρ_{12}) vary. (B) The epidemic size of an outbreak for killed vaccines when the probability that ruminants are vaccinated (ρ_{21}) and the probability that they receive repeated doses (ρ_{22}) vary. (C) The endemic number of RVFV among ruminants changes according to the the probability that ruminants are vaccinated (ρ_{11}) and the probability that they acquire immunity (ρ_{12}). In (D), the prevalence of RVFV among ruminants changes according to the the probability that ruminants are vaccinated (ρ_{21}) and the probability that they receive repeated doses (ρ_{22}).

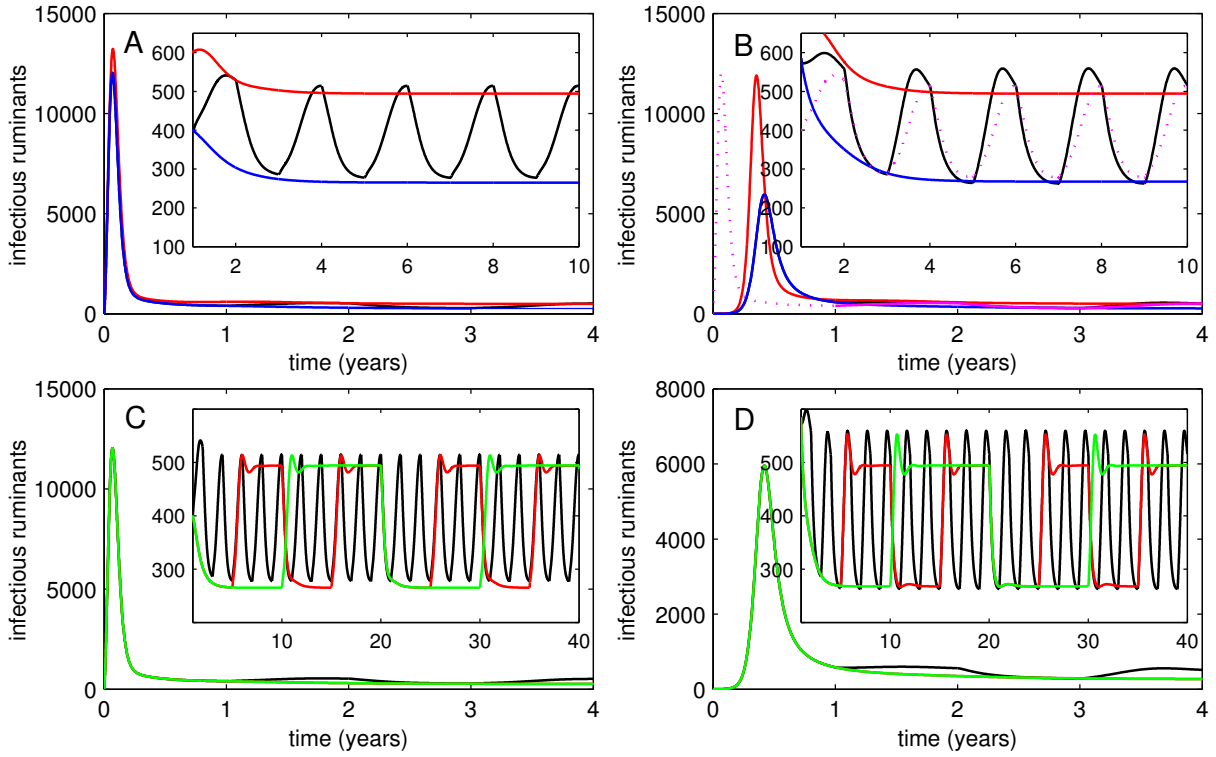

Figure 4. Periodic vaccination. We assume that periodic vaccination is described by $\rho_{11}(t) = 0.8, \quad i-1 \leq t \leq i$ and $\rho_{11}(t) = 0, \quad i \leq t \leq i+1$, where $i = 1, 3, 5, \ldots$. (A)-(B) show numbers of infectious ruminants due to periodic vaccination of live and killed vaccines, respectively (red trace = no vaccination, blue trace = constant vaccination, black trace = periodic vaccination: 1 year vaccination-1 year no vaccination-1 year vaccination). (C)-(D) show infectious numbers of ruminants due to periodic vaccination of live and killed vaccines (respectively) when vaccination periods vary (black trace = 1 year vaccination-1 year no vaccination-1 year vaccination, red trace = 3 year vaccination-3 year no vaccination-3 year vaccination, green trace = 5 year vaccination-5 year no vaccination-5 year vaccination).

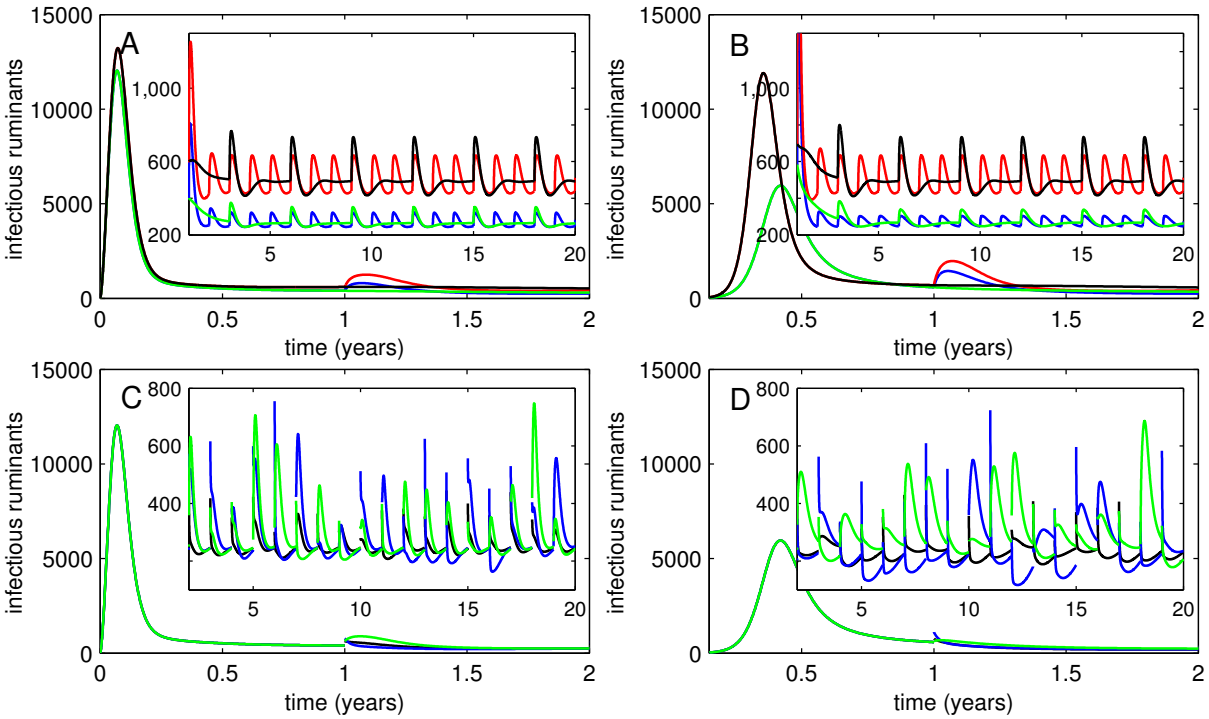

Figure 5. Recruitment of ruminants. (A)-(B) show the number of infectious ruminants corresponding to introduction of susceptible ruminants into areas where live or killed vaccines are used, respectively (red trace = with no vaccination and every year recruitment, black trace = with no vaccination and every three year recruitment, blue trace = with vaccination and every year recruitment, green trace = with vaccination and every three year recruitment). ruminants. (C)-(D) show the number of infectious ruminants corresponding to consumption and introduction of ruminants in each disease status in each year randomly for live and killed vaccines, respectively (black trace = fewer consumed ruminants and more numbers of recruited ruminants with immunity, blue trace = more consumed ruminants and more numbers of recruited ruminants with immunity, green trace = fewer consumed ruminants and fewer numbers of recruited ruminants with immunity).

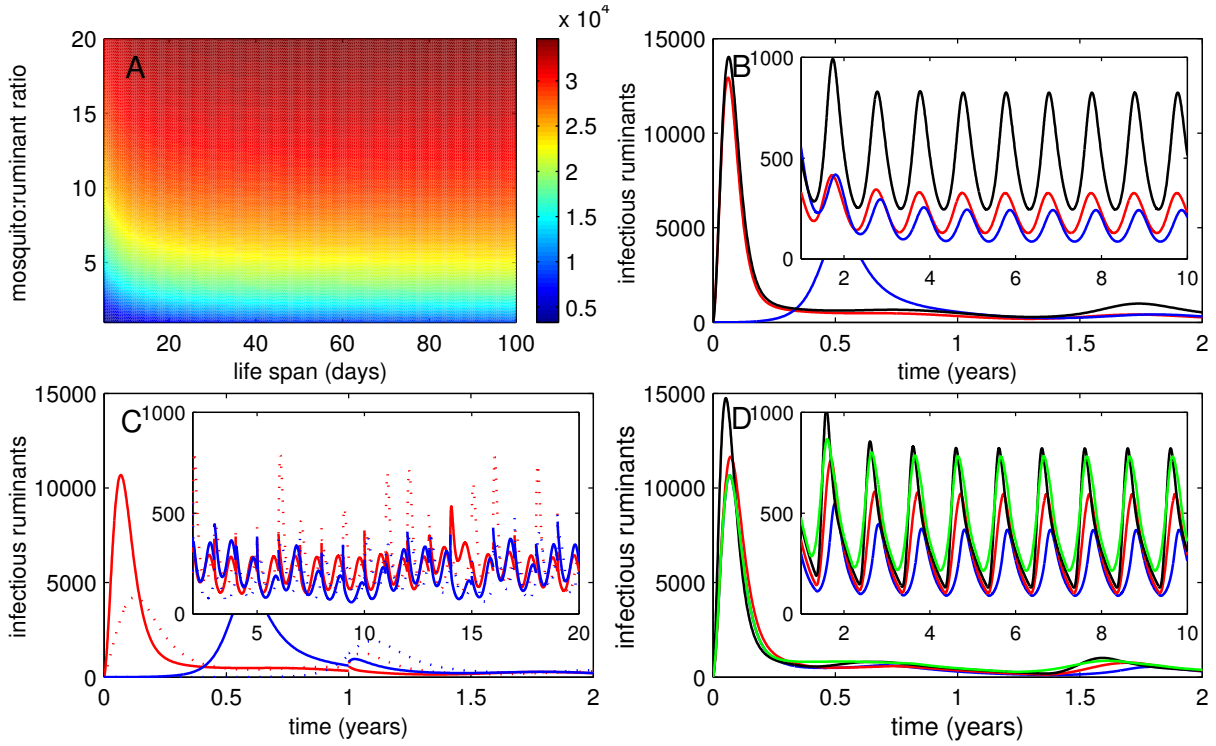

Figure 6. Mosquito activity. (A) The epidemic size of an outbreak according to changes in the mosquito lifespan and the mosquito:ruminant ratio. (B) The number of infectious ruminants changes according to the seasonal abundance of mosquitoes. (C) Changes in numbers of infectious ruminants relating to introduction of ruminants in each disease status in every year randomly (with fewer consumed ruminants during a feast and fewer numbers of recruited ruminants with immunity) during high and low mosquito activities for live and killed vaccines (red and solid trace= introduction of ruminants during low mosquito activities for live vaccines, red and dotted trace = introduction of ruminants during high mosquito activities for live vaccines, blue and solid trace = introduction of ruminants during low mosquito activities for killed vaccines, blue and dotted trace = introduction of ruminants during high mosquito activities for killed vaccines). (D) Changes in numbers of infectious ruminants relating to seasonal vaccination of live vaccines when the mosquito:rumiant ratio peaks during a rainy season ($k_0 = 2$) and is less abundant in other seasons ($k_0 = 2$) (blue trace = vaccination is not implemented in a rainy season which lasts 4 moths, red trace = vaccination is implemented in a rainy season which lasts 4 moths, green trace=vaccination is not implemented during a rainy season that lasts 6 moths, black trace=vaccination is not implemented in the areas).