The environmental limits of Rift Valley Fever revealed using eco-epidemiological mechanistic models

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Vector-borne diseases (VBD) of humans and domestic animals are a significant component of the global burden of disease and a key driver of poverty. The transmission cycles of VBDs are often strongly mediated by the ecological requirements of the vectors, resulting in complex transmission dynamics, including intermittent epidemics and an unclear link between environmental conditions and disease persistence. An important broader concern is the extent to which theoretical models are reliable at forecasting VBDs, as infection dynamics can be complex and the resulting systems highly unstable. Here, we examine these problems in detail using a case study of Rift Valley Fever (RVF), a high-burden disease endemic to Africa. We develop an eco-epidemiological, compartmental, mathematical model coupled to the dynamics of ambient temperature and water availability and apply it to a realistic setting using empirical environmental data from Kenya. Importantly, we identify the range of seasonally-varying ambient temperatures and water body availability that leads to either: the extinction of mosquito populations and/or RVF (non-persistent regimes), or to the establishment of long-term mosquito populations and consequently the endemicity of the RVF infection (persistent regimes). Instabilities arise when the range of the environmental variables overlaps with the threshold of persistence. The model captures the intermittent nature of RVF occurrence, explained as low-level circulation under the threshold of detection, with intermittent emergence sometimes after long periods. Using the approach developed here, opens up the ability to improve predictions of the emergence and behaviors of epidemics of many other important vector-borne diseases.

Rift Valley Fever | vector-borne diseases | zoonosis | cross-species transmission | stability analysis | Floquet analysis | viral haemorrhagic fever

Vector-borne diseases form an important class of infectious diseases, with over one billion human cases and one million human deaths per year (1) and are a significant contributor to global poverty. Current patterns of VBD occurrence are likely to change in future due to the accelerating rate of global climate and other environmental change that is predicted over the next century (2). Climate and land-use change and globalization are expected to affect the geographic distribution of arthropod species (3) through a variety of mechanisms, such as: changes to the variability in weather conditions altering survival, reproduction and biting rates of the vectors; changes to the availability of water bodies via, for instance, new irrigation patterns and dam constructions, creating new habitats for disease-competent vectors; human mobility and animal trade increasing the opportunity for vectors to reach and establish in new areas. Pathogen ecology is influenced by climate and weather too, for instance temperature, affects both the susceptibility of vectors to infection and pathogen extrinsic incubation periods, which usually requires pathogen replication at ambient temperatures (see *e.g.* (4, 5)). From here on we refer to 'ambient temperature' as 'temperature'.

These issues provide the basis of the work reported here. We focus on Rift Valley fever (RVF), an important mosquito-borne viral zoonosis. The causative virus is responsible for major epidemics in Africa and its range appears to be expanding, as demonstrated by phylogeographic analysis (6) and recent epidemic occurrence in Saudi Arabia and Yemen (7–10). Furthermore, concern has been raised about the potential for environmental/climatic changes causing increased impact of RVF in endemic areas or facilitating its spread to new regions of the of the world (10–12). RVF virus (RVFV) has a significant economic impact on the livestock industry in Africa, and can cause fatal disease in humans (13).

RVFV has a complex, multi-species epidemiology and is transmitted by biting mosquitoes, and occasionally directly by animal body-fluids. Infected mosquitoes transmit RVFV when taking a blood meal, potentially infecting a wide range of species. The disease is most significant in domestic ruminants, although wild animals (*e.g.* buffalos (14) and rodents (15)) might play an important role as reservoir hosts. Although more

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Significance Statement

Vector-borne diseases represent complex infection transmission systems; previous epidemiological models have been unable to formally capture the relationship between the ecological limits of vector species with the dynamics of pathogen transmission. By making this advance for the key disease Rift Valley fever, we are able to demonstrate how seasonally-varying availability of water bodies and ambient temperatures dictate when the mosquito vector populations will persist and, importantly, those sets of conditions resulting in stable oscillations of disease transmission. Importantly, under the latter scenario, short-term health control measures will likely fail, as the system quickly returns to the original configuration once the intervention stops. Our model, therefore, offers an important tool to better understand vector-borne diseases and to design effective eradication programmes.

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than 40 mosquito and midge species are known to be capable of transmitting RVFV ([16]), *Aedes*, *Mansoni* and *Culex* sp. are thought to be the most important for virus transmission to livestock and people.

Climatic drivers, such as temperature and rainfall, have a strong impact on the complex ecology of both RVFV and its vectors ([17]–[20]). Thus, the epidemiology of RVFV is likely to be strongly impacted by climate change ([21]). Other environmental, cultural and socio-economic factors, such as gathering of large numbers of people and domestic animals during religious festivities, have relevant implications for the infection dynamics of RVFV, including driving epidemics ([22]–[25]).

The complex features of RVFV infection dynamics have led to many studies. Empirical statistical approaches have identified key environmental variables, *e.g.* temperature and rainfall, that are associated with disease epidemics, enabling disease risk to be mapped ([11], [18], [19], [22], [23], [25]–[35]). Mechanistic models have added crucial insights for understanding links between disease transmission and the environment, by exploring the impact of seasonality and studying the processes leading to epidemic transmission ([24], [36]–[52]). Despite progress, these approaches are still subject to important limitations: the earlier mechanistic models do not incorporate seasonality; most models tend to include either only rainfall or temperature as contributing factors; if included, seasonality is usually incorporated only as an *ad hoc* periodic variation in the response (*e.g.* oviposition rate), rather than in the causative variable, undermining the realism of the approaches.

A further critical limitation of these studies is that they rely on rainfall data. In empirical statistical approaches, rainfall is often considered a 'predictor variable' (with the commonly associated problem of collinearity ([53])). In mechanistic models, rainfall is usually a proxy for breeding sites. In complex hydrogeological models, rainfall is merely an input to represent water bodies; the major problem with this approach is that the dependence of RVFV on rainfall varies widely across countries and ecoregions, due to, *e.g.* different types of terrain, evaporation rates, delay between rainfall occurrence and establishment of water bodies, etc.

To overcome these limitations, we developed a unified, process-based model built on a realistic representation of how the dynamics of water bodies obtained from satellite images (rather than rainfall) and temperature influence the ecology of the primary mosquito vectors and the epidemiology of RVFV. A critical feature of using this approach is our ability to investigate, for the first time, the combined impact of seasonalities in both water availability and temperature, allowing us to: i) capture the influence of seasonal patterns of temperature and water bodies on the quantitative transmission dynamics of RVFV; ii) quantify the environmental drivers that lead to regional endemicity of RVFV; iii) assess if transovarial transmission in *Aedes* sp. (the only species of mosquitoes for which ovarian transmission is known), is necessary for RVFV persistence; iv) isolate the mechanisms allowing virus re-emergence after long periods of inactivity in endemic regions ([43], [54]); v) identify if, and under which conditions, the complex patterns of RVFV epidemics resemble chaotic behavior, *i.e.* the system being highly sensitive to initial conditions ([55]), rendering disease predictions difficult.

Analysis

Our analyses were conducted within two main contexts: a theoretical case, represented by a simple sinusoidal variation of the surface area of water bodies and of temperature (represented by equations Eq. (6) and Eq. (7)) and a realistic situation, where we used empirical data for Kenya (namely: spatially averaged temperature ([56]) and the total surface area of water bodies over the entire territory divided by the surface of Kenya; SI Appendix, S1 Text). Here and throughout, we refer to these two situations as 'theoretical model' and 'realistic model'. We first ran the theoretical model by systematically changing the mean annual temperature and mean annual surface area of water bodies, (*i.e.* parameter T_m and S_m^P in equations Eq. (6) and Eq. (7)), for each simulation we ascertained whether or not the predictions result in sustained fluctuations in populations of *Culex* sp. or *Aedes* sp. (the dominant vectors in Kenya ([57])), or in the prevalence of RVFV in livestock. All other parameters were kept the same and the surface area of water bodies and temperature were allowed to fluctuate in phase with annual periodicity (*e.g.* the parameters $\phi_S = \phi_T = \pi$ in equations Eq. (6) and Eq. (7), but see SI Appendix, S1 Text for a situation when this constraint was relaxed). We conducted analyses in both the theoretical and realistic models using different initial conditions and numbers of livestock. How frequently the surface area of water bodies change is likely to have an impact on mosquito populations. Thus, for the theoretical model, we varied the frequency of water bodies body surface area fluctuation (*i.e.* ω_S equations Eq. (6) and Eq. (7)) while ensuring the same overall annual surface area of water bodies. In order to investigate the intermittent nature of observed RVF epidemics, we assumed that, when the mean number of infected livestock is below a certain threshold the epidemic is not detected. This is a reasonable assumptions considering the frequency of subclinical infections and the limited diagnostic facilities available in endemic areas. Cases detected within 30 days apart are assumed to be part of the same epidemic. We then ran the realistic model 100 times with the initial number of livestock and with infection prevalence in the livestock randomly drawn from uniform distributions (respectively $100 - 5000$ for the number of livestock and $5\% - 20\%$ for the infection prevalence). All other parameters were kept the same. The simulation was also run in the absence of transovarial transmission. In each case, we then estimated the periods of time during which RVFV was not detected. Predictions of the duration of inter-epidemic periods for the realistic model were compared with historical data of RVF epidemics which had occurred in Kenya, 2004 to 2013 obtained from the Global Animal Disease Information System, EMPRES-i ([58]).

Results

Influence of the seasonal patterns of temperature and water bodies on the quantitative dynamics of RVFV. The theoretical model shows (Fig. 1 and more details in Fig. S19 in the SI Appendix, S1 Text) that different amplitudes and frequencies of fluctuations in temperature and water availability within the system result in different disease patterns. It is possible, for example, that one or both mosquito species might go extinct; that there could be stable oscillations with one or more annual peaks in the mosquito population but in a RVFV-free situation; that there could be stable mosquito populations with sporadic
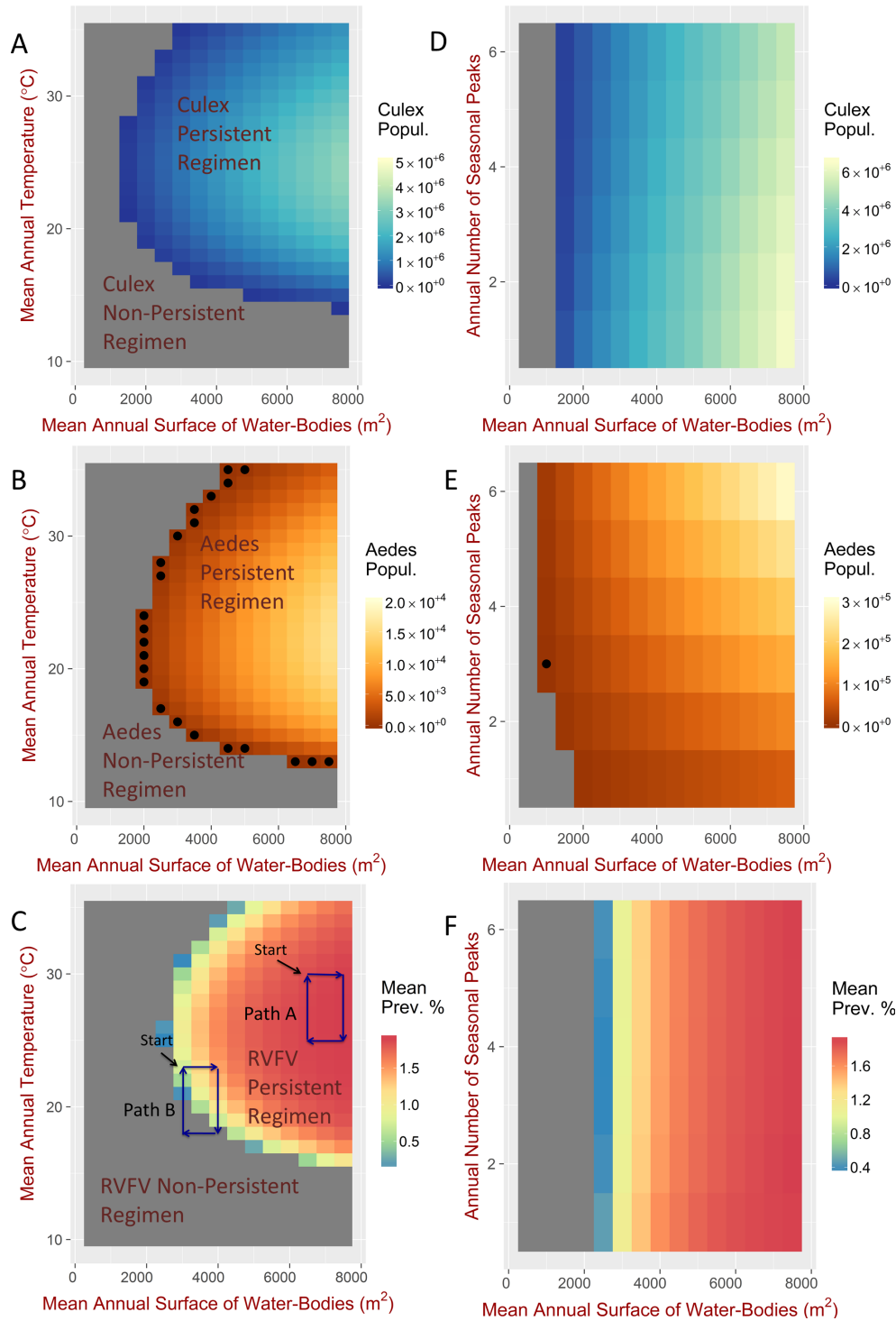
Fig. 1. Environmental constraints leading to persistent and non-persistent regimens mosquitoes and RVFV. Panel A-B-C. Impact of mean water bodies surface area and mean temperature on the population of mosquitoes and RVFV prevalence. Water bodies surface area and temperature are described by sinusoidal functions according to equation Eq. (6) and Eq. (7). The x−axis shows the mean water bodies surface area S_m^P while the y−axis the mean temperature T_m, which are the only parameters that are changed in the simulations while the frequency ($\omega_S = \omega_T = 2\pi/365$) and phase ($\phi_S = \phi_T = \pi$) are kept constant. Panel D-E-F. Impact of frequency of oscillations in water bodies surface area on the population of mosquitoes. Water bodies surface area is described by sinusoidal functions according to equation Eq. (6) with ($\phi_S = \pi$), while the temperature is kept constant ($T = 25°$). The x−axis shows the mean water bodies surface area S_m^P while the y−axis the annual number of seasonal peaks in water bodies surface area, which are the only parameters that are changed in the simulations.

The gray area corresponds to a region in the space of parameters where the mosquitoes population (panels A,B,D,E) or the yearly averaged infection prevalence in livestock (panel C and F) drops to zero after a transient phase (negative largest Floquet exponents of the linearized system around the null solution); the colored regions with no black dots, correspond to a region in the space of parameters where the mosquitoes population or the yearly averaged infection prevalence in livestock will always establish sustained oscillations after a transient phase (negative largest Floquet exponents of the linearized system around a periodic limit cycle solution), the intensity of the color correspond to the yearly average number of mosquitoes or infection prevalence in livestock. The black dots in panels B and E identify a region in the space of parameters where the solution is unstable (positive largest Floquet exponents, this because the time considered is too short for the solution to stabilize).

RVFV epidemics; or that RVFV might become endemic.

Quantifying the environmental drivers leading to regional endemicity of RVFV. The theoretical model predicts the existence of a temperature-dependent threshold in mean surface area of water bodies below which, mosquito populations and RVFV always fade out (grey areas in Fig. 1, which are referred to as 'non-persistent regime'). The model also showed the parameter space (*i.e.* the set of all possible combinations of values for the different parameters) resulting in a 'persistent regime', *i.e.* sustained oscillations in the vectors and RVFV (colored area in Fig. 1). The intensity of the color reflects the yearly averaged population of the mosquitoes or the yearly averaged prevalence of RVFV in livestock. The optimal conditions for mosquito occur when the mean body surface area is at its greatest and when the mean temperature $\approx 26°C$ for *Culex* and $\approx 22°C$ for *Aedes* (Figure 1). The prevalence of RVFV in livestock is predicted to be highest when temperature $\approx 26°C$. The ranges of mean annual temperature and mean annual water body surface area resulting in sustained fluctuations in mosquito abundance, in particular for *Aedes* sp., differ from those causing sustained oscillations of RVFV in livestock. There are some regions where RVFV endemicity is possible in the absence of *Aedes* sp. and there are a few situations where a persistent mosquito population does not support RVFV endemicity (see also Fig. S19 in the SI Appendix, S1 Text). Under a constant temperature, of $25°C$, the average abundance of *Culex* sp. decreases with increasing frequency of oscillation in water availability (Figure 1D). This is due to non-trivial interactions arising from particular mosquito population sizes at times when the surface of water bodies starts decreasing. In contrast, *Aedes* sp. abundance increases with the frequency of oscillations in water body surface area (Figure 1E). This is not surprising as, in contrast to *Culex* sp., the hatching of *Aedes* sp. eggs is driven by flooding and dessication cycles. In the extreme case of no water body fluctuation, *Aedes* sp. is expected to go extinct, although this does not always occur as a small proportion of *Aedes* eggs hatch spontaneously without dessication/flooding (59) (Fig. S20 in the SI Appendix, S1 Text). The domain of the RVFV persistent conditions is dependent on the abundance of livestock, N_L, in particular when this impacts on the biting and oviposition rate (Fig. S21-S23 in the SI Appendix, S1 Text). The intensity of the fluctuations in temperature and in the surface area of water bodies appear to have little impact on mosquito abundance and on whether RVFV becomes endemic (Fig. S24 in the SI Appendix, S1 Text).

When does the complexity of RVFV dynamics resemble chaotic behavior?. Stability refers to the property of an ecosystem to return to equilibrium if perturbed (55), or equivalently, that the system will always reach the equilibrium state regardless of the initial conditions. In the theoretical model, the equilibria are represented by extinction of mosquito species and/or RVFV infection (non-persistent regime) or, more or less complex, periodic oscillations (persistent regime). For the mosquito populations, Floquet analysis (see 'Material and Methods' and SI Appendix, S1 Text) demonstrates that the long term mathematical solutions are stable. For RVFV infection, numerical computations show that the solutions are stable once the initial conditions, *i.e.* the initial number of livestock, are fixed (Fig. S25 in the SI Appendix, S1 Text).
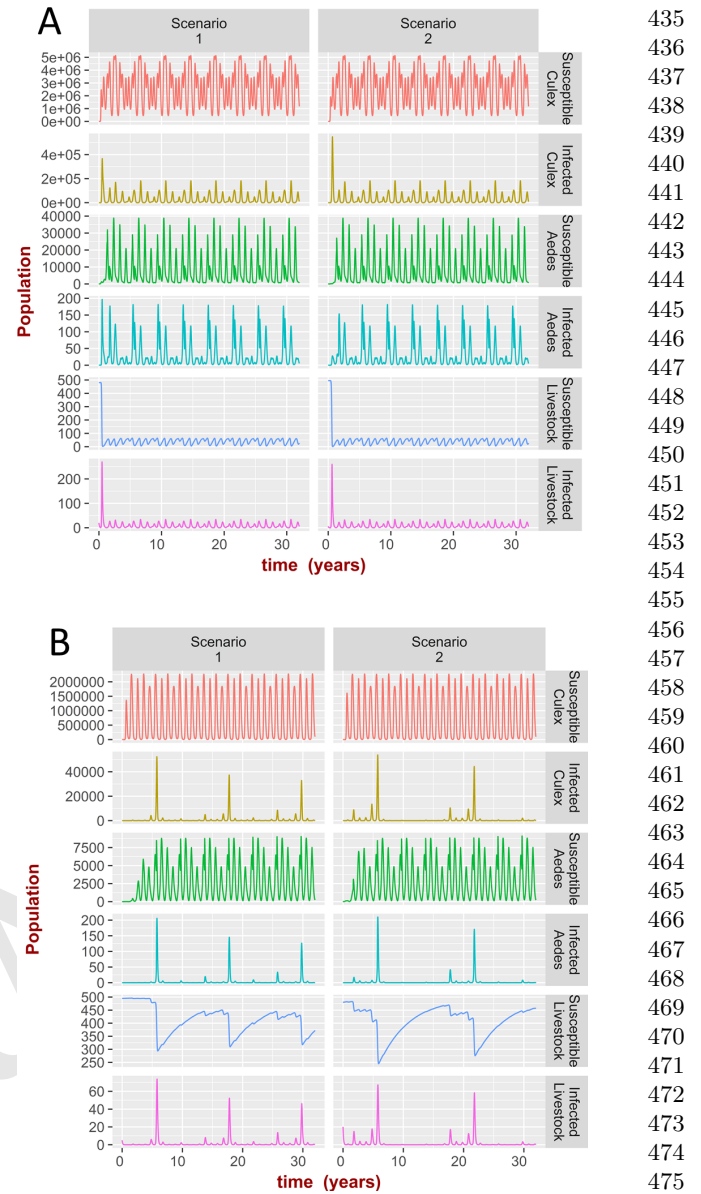

Fig. 2. During the time of simulation (32 years), the mean surface area of water bodies and mean temperature is cyclic changing according to path A and path B illustrated in bottom panel in Fig. 1.C; *i.e.* for path A: during the first year, the mean surface area of water bodies increases according to a stepwise function with four months interval (Fig. S27) from $6500m^2$ to $7500m^2$ and the mean temperature is constant at $30°$ followed by a second year with constant mean surface area of water bodies at $7500m^2$ while the mean temperature is decreasing according to a stepwise function with two months interval, from $30°$ to $25°$, during the third year the mean surface area of water bodies decrease according to a stepwise function with for months interval, from $7500m^2$ to $6500m^2$ and the mean temperature is constant at $25°$, followed by a fourth year when the mean temperature is increasing according to a stepwise function with two months interval, from $25°$ to $30°$ and the mean surface area of water bodies is constant at $6500m^2$; for path B: the dynamics is the same for path A but the range of the mean surface area of water bodies is between $3000m^2$ and $4000m^2$ and for mean temperature the range is between $18°$ and $23°$. A) Dynamics of mosquitoes population and RVFV infection in livestock when mean temperature and mean surface area of water bodies changes according to path A, for two different initial conditions: Scenario 1) Exposed and removed livestock and all mosquitoes stages are set to zero except for the susceptible and infected livestock $S_L = 495$ and $I_L = 5$ and mosquitoes eggs $O_C = 100$, $O_I = 100$ Scenario 2) As in scenario 1, but $S_L = 480$ and $I_L = 20$ and mosquitoes eggs $O_C = 100$, $O_I = 100$. The asymptotic behavior is the same in both scenarios. B) as in A) but the mean temperature and mean surface area of water bodies changes according to path B. The asymptotic behavior is different for the different scenarios.

Changing the initial number of livestock has no practical effect on the overall population of mosquitoes, when the impact of livestock on mosquito oviposition and biting rate is assumed to be negligible (*i.e.* for very large values of the parameter q as in this case, but see Fig. S23 in the SI Appendix, S1 Text, for other scenarios). The number of livestock, however, predictably impacts the temporal patterns of infected mosquitoes and infected livestock (Fig. S25 in the SI Appendix, S1 Text) and the system can no longer be considered stable if the number of livestock is externally perturbed. Accordingly, animal movements, including the immigration of infected animals, might have a significant impact on the pattern of RVFV infection. Similar behavior is observed for the realistic model, where simulations show that, regardless of the initial conditions, the system approaches the same asymptotic limit, with only the initial number of livestock having a direct impact on the patterns of infections (Fig. S25 in the SI Appendix, S1 Text). The property that the system always reverts to the same asymptotic solution (after fixing the initial number of livestock), is not general. An important counter-example is shown in Figure 2 (and S26 in the SI Appendix, S1 Text). In this simulation experiment we consider the two scenarios illustrated by Path A and Path B in Fig. 1.C; first when the mean temperature and mean surface area of water bodies are always within the RVFV persistent regime, secondly when these values transit from RVFV persistence to RVFV non-persistence and then back again. To do so, we divided the entire time (32 years) into 8 cycles; each 4−year cycle (described either by Path A or Path B in Fig. 1.C), consists of 4 intervals of one year each (represented by the segments in the paths). For each interval, we let the mean values T_m or S_m^P in equations Eq. (6)-Eq. (7) change year by year (Fig. S27 in the SI Appendix, S1 Text). For each scenario we then considered two different situations, by imposing different the initial condition in the infection prevalences (but the same total number of livestock). When the mean temperature and mean surface area of water bodies varies within the RVFV persistent regime (Path A), the system reaches the same limit irrespective of the different initial conditions (Fig. 2.A). In contrast, for the situation described by Path B, different values of the initial infection prevalence lead to qualitatively different solutions (Fig. 2.B), a phenomenon resembling chaotic systems observed in meteorology. This phenomenon can be stronger for different parameter values, leading to a situations when the overall mosquito populations, as well as their infection prevalences, are asymptotically different (Fig. S26 in the SI Appendix, S1 Text).

Is transovarial transmission in Aedes necessary for RVFV persistence?. The simulations of RVFV dynamics demonstrated persistence in *Culex* sp. in the absence of *Aedes* mosquitoes (Fig. 3) over 15-years in the realistic model. The numerical simulation shows, persistent patterns of RVFV occur in absence of *Aedes* sp. In the theoretical model, the use of Floquet theory should prevent the problem of infection persistence at unrealistic low levels ('atto-fox problem' (60)), as the theory focuses on the stability of the precise zero, or periodic, solution (although here the stability of RVFV was studied only numerically). In general, random extinctions of RVFV preclude persistence of infection, although one could argue that deterministic models mimic the fact that random extinctions are compensated by random immigration of infected mosquitoes or livestock.
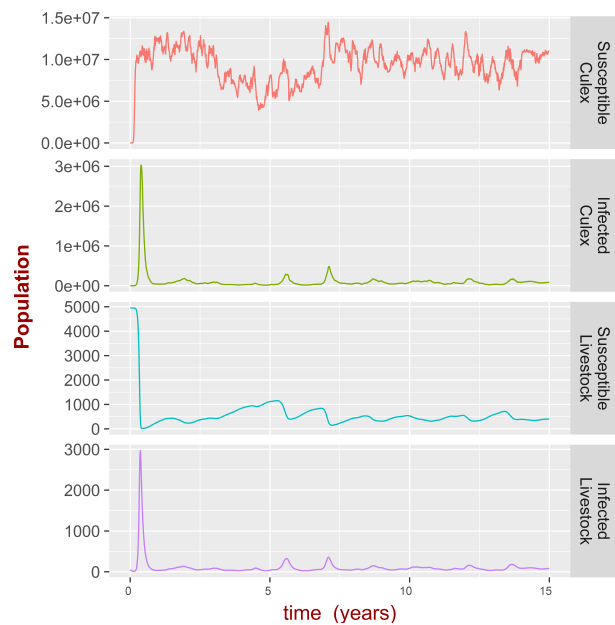
Fig. 3. Assessing the impact of transovarial transmission. Dynamics of *Culex* sp. population and RVFV infection in livestock in absence of *Aedes* sp. population for the realistic model. The theoretical cases is exemplified by Fig. S19.B in the SI Appendix, S1 Text.

Incorporating demographic stochasticity and spatial immigration would address this concern. Taking all this into account, we cautiously conclude that the transovarial transmission of RVFV in *Aedes* sp. is not a prerequisite for RVFV persistence over time, although the models provide no evidence to discount this as an important (49), transmission route in reality.

Isolate the drivers enabling the virus to re-emerge after long periods of inactivity in endemic regions. Here we assumed that when the mean number of infected livestock is below a certain threshold, chosen to be 50, (see also SI Appendix, S1 Text for 5 infected animals and 1% of infection prevalence), the epidemic is not detected by routine surveillance. The patterns of the distributions of these disease-undetected times (Fig. 4) are similar for the situations when both mosquitoes species are present and when *Aedes* sp., and thus transovarial transmission, is absent. The empirical inter-epidemic periods observed in Kenya from 2004 to 2013 (58) are shown for comparison. The similarity of the patterns suggests a strong impact of external drivers and variation in immunity in livestock populations, compared to the impact of the mosquito species. Both distributions are multimodal (Fig. 4) with several peaks occurring, interestingly several small peaks occur over long time periods (> 10 years). This shows that RVFV can circulate in the system at very low, undetectable, levels, emerging unexpectedly after very long time periods. For lower level of threshold (Fig. S29 in the SI Appendix, S1 Text), the probability of observing long inter-epidemic periods is smaller. This further highlights the importance of including stochasticity in the diagnostic (the detection threshold). As discussed above, demographic stochasticity allows for the extinction of the infection, and other factors, such as spatial immigration, would allow re-emergence. Incorporating this mechanism would likely have a detectable impact on patterns of the inter-epidemic periods.
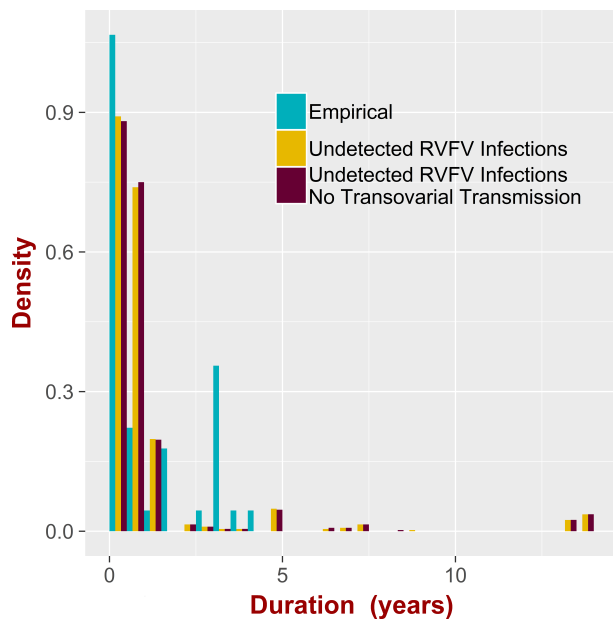
Fig. 4. Assessing the intermittent nature of RVFV. Histogram representing the density of duration of inter-epidemic periods for empirical data and for the model when *Aedes* spp. is absent (origin of figure-4 due to only to undetected cases) and when both mosquitoes species are present (origin of figure-4 due to undetected cases and transovarial transmission).

Discussion

We identified the range of seasonally varying temperatures and water body extent leading either to extinction of mosquito populations and/or RVFV or to established mosquito populations and endemicity of the infection. These results allow prediction of future geographic distribution of RVFV due to changes in environmental and climatic conditions across the globe.

To achieve this, we developed a process-based mathematical model, which unifies environmental factors, the ecology of mosquitoes and the epidemiology of RVFV.

A unified framework for the dynamics of VBDs. A key advantage of the current model is its conceptual simplicity, with the undeniable complexity of the system reduced to a few fundamental factors: surface area of water bodies governing mosquito oviposition rates, and temperature affecting mosquito developmental rates, their survival and biting rate as well as the extrinsic incubation period of RVFV. The impact of these parameters cascades on the dynamics of the mosquito population and thus RVFV. The seasonality of mosquito abundance and infection prevalence is largely governed by the seasonality in water body surface area and temperature. The resulting patterns, however, are not trivial due to the non-linearity of the system; even in a theoretical system represented by simple sinusoidal variation of water body surface area and temperature, the different combinations of these results in qualitatively different regimes, including one or both mosquito becoming extinct, a RVFV-free scenario but with established mosquito populations, or with sustained oscillations of mosquito abundance and RVFV prevalence (in mosquitoes and livestock) with one or more annual peaks. The modular nature of the model facilitates its calibration and validation. For example, the mosquito model can be tested in an RVFV-free situation, only subsequently including the effects of the disease.

Environmental conditions allowing established mosquito populations and viral persistence. The abundance of mosquito eggs is ultimately constrained by the maximum density of eggs (*i.e.* number of eggs per unit surface area) and the surface area of water bodies, resulting in a carrying capacity that results in a stable mosquito population irrespective of initial conditions. In the realistic scenarios, this was demonstrated numerically; in the theoretical systems we proved the stability of the system by using Floquet analysis. This demonstrated a lower threshold in mean water body surface areas below which the mosquito populations will go extinct otherwise it will result in sustained oscillation. The value of this threshold depends non-monotonically on the mean temperature and it is confined between a lower and upper values, reflecting the fact that mosquitoes do not survive in very cold or very dry hot temperatures. The analysis also showed the importance of the frequency of fluctuations in water body dynamics, especially for *Aedes* sp. Similar thresholds in temperature and water bodies occur for the persistence of RVFV in livestock, reflecting the geographic distribution of the disease. Here, livestock numbers were also critical. The bio-physical interpretation of stability analysis is extremely important. For example, stable oscillations in the mosquito population imply that, unless there is a permanent change in the drivers (*e.g.* average surface area of water bodies), any temporary measure aiming to reduce the mosquito population, *e.g.* chemical control, will not result in a permanent solution as mosquito abundance is expected to return to the original values once application of control measures stops. Similarly, if mosquitoes are imported into a region whose temperature and water body parameters are in the persistent regime, then they will become established in this new environment.

Intermittent nature of RVFV and the problem of predictability. Epidemics of RVFV are intermittent and typically not very predictable [43, 54]. Severe epidemics are provoked by flooding after protracted periods of drought. Transovarial transmission in *Aedes* mosquitoes is a mechanism of RVFV persistence [61] and a possible explanation for the intermittent nature of RVFV epidemics as presumably infected *Aedes* sp. eggs can survive for several years. Another explanation is that RVFV is always circulating in the population, perhaps in a cryptic reservoir [14, 15, 62], at very low level and not detected. This is supported by evidence of inter-epidemic RVFV seropositivity among humans and animals [63, 64] and the indication of sub-clinical infection in livestock [65]. Our model suggests that transovarial transmission is not necessary for inter-epidemic persistence of RVFV and the infection may continuously circulate at low and largely undetectable levels in between irregular epidemics; change in immunity in livestock population is playing an important role in the irregularity of the infection patterns. This result is strictly valid, however, when all animals and mosquitoes are well connected (*e.g.* through animal movement), as our deterministic model is based on the assumption of uniform mixing. Our theoretical model shows that, once the initial number of livestock is fixed, the solution is stable and long term behavior can be accurately predicted even if the initial conditions, such as the exact number of infected animals or the abundance of mosquitoes at a given time, are not known. If the number of

livestock, however, is perturbed, the solutions are qualitatively and quantitatively different even if all other conditions are kept identical. Thus, for reliable predictions accurate information on the demography of livestock is necessary (for the impact of the livestock size on infection see SI Appendix, S1 Text). In some situations, however, this is not sufficient. The mean surface areas of water bodies and temperatures can change (as in Kenya, when mean surface area of water bodies decreased during $2003-2007$, Fig. S4 SI Appendix, S1 Text), and transit from the persistent to non-persistent regimen and vice-versa. In such situations, the system becomes highly sensitive to the initial values of infection prevalence, a situation that resembles chaotic behavior. Thus the irregularity of the system can arise even from small variations in the infection prevalence, due to, for example, immigration of a few infected livestock. Clearly, variations in the demography of livestock (such as occur in festivals (24)) and transitions across persistent and non-persistent regimens are additional causes of figure-4 in RVFV.

A programme for future work. This work identified important challenges that could be addressed by further theoretical work and model-guided fieldwork. Fieldwork can be designed to test well-defined hypotheses that emerge from the model, such as the predicted larger abundance of *Aedes* sp. in regions where water bodies are fluctuating more frequently and the existence of thresholds in surface area of water bodies and temperature confining the domain of the persistent regimens for mosquito species and RVFV infection. Further experiments to gauge the impact of livestock density on mosquito oviposition and biting rates (66) are crucial as this will have an important effect on the mosquito population and on patterns of RVFV infection (see SI Appendix, S1 Text). In most cases we focus on one host only. Co-presence of multiple hosts can dilute or amplify the disease. Further investigations on host feeding preference (67) and the relationship between mosquito abundance and host population size is critical to estimate this effect (68). A challenging point is the large uncertainty associated with many parameter values, in particular the life-history parameters of mosquitoes stage are often based on laboratory conditions and inferred for different species of mosquitoes. Theoretical works like this can steer future fieldwork and experimentation to reduce the knowledge gaps that emerged from the model.

The potential impacts of multiple hosts, including wildlife hosts (*e.g.* buffalo) also needs to be investigated. We assumed uniform mixing between mosquitoes and livestock. As a result, the predicted patterns of infection in *Aedes* sp., *Culex* sp. and livestock are qualitatively similar. The model ought to be generalized to incorporate heterogeneity occurring in nature. Furthermore, the model needs to be refined to incorporate the impact of vegetation and natural predators on the ecology of mosquitoes. This could be done, for example, by allowing the birth and mortality rate to depend on such factors and calibrating the model accordingly. The presence of livestock and other animals might attract mosquitoes from neighbor areas, *via* CO_2 emission, resulting in a density dependent vector-to-host ratio relationships (68). In general, climate change is expected to cause not only an increase in the average temperature, but also rainfall intensity and frequency. Climate projections can be readily incorporated in the model for a more accurate analysis of the impact of climate change on the ecology of mosquitoes and the epidemiology of RVFV. The impact of animal movement is an an other crucial driver of RVFV (34) (see also discussion in (69)). Future research should address, for instance, how the epidemiology of RVFV changes in the presence of livestock immigration and how this is affected by the size of these imports and the number of infected animals in each batch.

Our analysis was done using a deterministic model, but environmental stochasticity and external periodic drivers (*e.g.* seasonality in temperature and surface area of water bodies) can resonate with the natural frequencies of the eco-system (70) with large effects on the ecology of mosquitoes and the epidemiology of RVFV. Furthermore, patterns of the inter-epidemic periods should be assessed by taking into account stochastic variability in demography and diagnostic at different spatial settings. These are crucial questions to consider in future research. Extension of the model to include spatial variability is the natural progression of this work. By using high spatio-temporal resolution of water bodies (71), temperature (56), type of vegetation data, and animal census, the model could be carefully calibrated to assess whether or not the environmental variables are within the persistent regimens. Then the approach could be used to generate a map of potentially endemic regions for RVFV or other VBDs in order to plan interventions more effectively (*e.g.* aiming at long term control of environmental conditions, such as reducing the size of water bodies, in endemic areas and short term measures, such as limiting animal movement, in non-endemic areas). If the environmental variables are at the interface between persistent and non-persistent regimens, then more robust uncertainty and sensitivity analysis is required, exploring not only the space of parameters, but also the plausible distribution of the initial conditions, such as livestock population and its infection prevalence. This also raises important practical and theoretical questions on the reliability of statistical models based on presence/absence of cases, when the epidemiology is subject to chaotic behavior.

Materials and Methods

The model combines an ecological, stage-structured, population dynamics model for the *Aedes* sp. and *Culex* sp. with an epidemiological Susceptible-Exposed-Infectious-Recovered (SEIR) compartmental model for the livestock and a Susceptible-Exposed-Infectious (SEI) model for the two mosquito populations. For simplicity we assume only one host, although the model can be readily extended to include multiple heterogeneous hosts (*e.g.* goats, cattle, sheep). The stage-structured, population dynamics of the mosquitoes is largely based on the model of Otero *et al.* (72), which includes the effect of temperature on the development rate of the mosquitoes. Important additions to Otero *et al.*'s model are: i) the dependence of the oviposition process on the water bodies surface; ii) the separation of *Aedes* sp. eggs in mature and immature eggs; iii) the dependency of the number of eggs per batch on the density of livestock. Below we emphasize the novel aspects of the model, while a detailed formulation of the framework is presented in the SI Appendix, S1 Text.

Eco-epidemiological model. The *Culex* sp. populations consist of: eggs (O_C), larvae (L_C) pupae (P_C) nulliparous female, *i.e.* female adults not having laid eggs (C_1), flyers (F_C), and female adults having laid eggs C_2; the *Aedes* sp. consist of:

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immature and mature eggs (O_I and O_M), larvae (L_A), pupae (P_A), nulliparous female (A_1), flyers (F_A), and female adults having laid eggs A_2. Adult male mosquitoes are not explicitly included, and only one half of the emerging adults are females. Once the first gonotrophic cycle (*i.e.* feeding on blood meal and laying of eggs) ends, the nulliparous female becoming a flyer (F_C and F_A) in search of breeding sites followed by a series of cyclic transitions, regulated by the second gonotrophic cycle to the adult stage (C_2 and A_2) and back to the flyer status (F_C and F_A).

Temperature dependent development rates for the gonotrophic cycles, in the limit of infinitely available blood meal, were based on parametrization presented in the literature (42), the other stages were modeled according to Schoolfield's simplification of Sharpe and DeMichele's model for poikilotherm development (73) based on data from (74) (SI Appendix, S1 Text and table S6). Lifestage-specific mortality rates for *Culex quinquefasciatus* and *Aedes aegypti* were extracted from data collected under standard laboratory conditions in (74). Ordinary least squares regression models were fitted with mortality rate as the response variable and temperature ($15-34^\circ C$) as the explanatory variable (Figs. S17-S18 and SI Appendix, S1 Text). Besides the daily mortality in the pupal stage, there is an additional mortality associated with the emergence of the adult (72).

The population dynamics of eggs is regulated by the availability and dynamics of suitable breeding sites, *i.e.* temporary water bodies (dambos) (Fig. S13-S14 in the SI Appendix, S1 Text) typically formed by heavy rainfall. In contrast with *Culex* sp., *Aedes* sp. lay their eggs in the moist soils above mean high water surrounding the water body (SI Appendix, , Figure S14). According to (75), the average time for egg deposition is $t_{dep} = 0.229$ days in laboratory conditions, which are assumed to be ideal conditions; at field scale the mosquitoes need to search for a suitable breeding site reducing the oviposition rate, *i.e.* number of times a flyer lay a batch of eggs per time unit. Thus the oviposition rate for is modeled as: $\eta^{\text{Culex}} = \eta^{\text{Aedes}} \approx \sum_P S^P(t)/(\mathcal{A} t_{dep})$ where $\mathcal{A}$ (assumed to be the same for both species of mosquito) corresponds to the typical size of the terrain scanned by a flyer to detect suitable breeding sites, and $S^P(t)$ is the overall surface, at time t, of the breeding sites dispersed in a region of area $\mathcal{A}$. This region is estimated as $\mathcal{A} \approx 1E6 - 2E6\ m^2$ based on some indication that the spatial range of the activity of mosquitoes would be up to $1500\ m$ to the nearest suitable water body (76), the time varying surface $S^P(t)$ was obtained by satellite images (71). For simplicity, the contribution of small, artificial containers with water such as tires, flower pots, tin cans, clogged rain gutters, etc. is not included. This is justified by the fact that common species of the genus *Aedes* involved in the transmission of RVFV, such as *Aedes mcintoshi*, *Aedes circumluteolus*, *Aedes ochraceus*, breed in temporary grassland depressions (dambos) (17). Breeding sites already occupied by eggs prevent further ovipositions, we therefore introduced a carrying capacity in the egg load rates, *i.e.* number of eggs laid by all flyers per time unit, as: $\xi^{\text{Culex}} = \tilde{b}_C \eta^{\text{Culex}} \left(1 - \frac{O_{Culex}}{K_C}\right)$ and $\xi^{\text{Aedes}} = \tilde{b}_A \eta^{\text{Aedes}} \left(1 - \frac{O_{Aedes}}{K_A}\right)$, where O_{Culex} and O_{Aedes} are the total number of eggs for *Culex* sp. and *Aedes* sp. eggs already laid, in the first case $O_{Culex} = O_C$, in the second cases it is the sum of mature and immature eggs irrespective of their infected status; $\tilde{b}_C$ and $\tilde{b}_A$ are the number of eggs

per batch, and the carrying capacities K_C and K_A take into account that the maximum number of eggs that can be laid over a water body is limited by its surface, $S^P(t)$, namely: $K_C \approx \sum_P \rho_C \kappa^{\text{Culex}} S^P(t)$ and $K_A \approx \sum_P \rho_A \kappa^{\text{Aedes}} S^P(t)$, where ρ_C and ρ_A are the density of eggs per surface unit (either water for *Culex* sp. or soil for *Aedes* sp.), $\kappa^{\text{Culex}} S^P(t)$ and $\kappa^{\text{Aedes}} S^P(t)$ represent the fraction of the breeding site suitable for eggs deposition and survival; for *Culex* sp. this corresponds the an inner area around the edge of the water body and for *Aedes* sp. is the outer moist soil around the water body (here we assumed that both surface areas are proportional to the total surface area of the water bodies). In addition, mosquitoes cannot produce eggs without ingesting blood meals, thus following the same argument presented in (66) for triatomines, the numbers of *Culex* sp. and *Aedes* sp. eggs per batch, $\tilde{b}_C$ and $\tilde{b}_A$, are rescaled respectively by a factor $b_C/(1 + m_C/q)$ and $b_A/(1 + m_A/q)$ where b_C and b_A are the maximum number of *Culex* sp. and *Aedes* sp. eggs produced per batch in the limit of infinite resources, m_C and m_A is the calculated vector-to-host ratio (here assumed to be 1% of the total number of mosquitoes divided the number of livestock, SI Appendix, S1 Text) and q the particular vector-to-host ratio for which vector fecundity is divided by two (but if both mosquitoes species are present than we consider the total vector-to-host ratio $m_C + m_A$). Based on the same argument (66), the rates of gonotrophic cycles, which are assumed to be the same as the biting rates, was rescaled in the same manner. Accordingly, in absence of host, *i.e.* no blood-meal, the number of eggs per batch and the biting rate drops to zero.

Aedes sp. eggs require a minimum desiccation period T_d, after this period they are ready to hatch provided that they are submerged in water, although 19.7% of newly embryonated *Aedes* sp. eggs hatch spontaneously without flooding (59), *Aedes* sp. eggs can survive dessication for several years. Therefore we distinguish two egg stages O_I and O_m, with development time of newly laid eggs O_I conditioned to:

$$\frac{1}{\theta_{O1}^{\text{Aedes}}} \approx \max\left(T_d, \frac{1}{\theta_{O}^{\text{Aedes}}[T(t)]}\right) \quad [1]$$

where $\theta_O^{\text{Aedes}}[T(t)]$ is the temperature dependency of development rate of the eggs (72) (SI Appendix, S1 Text, equations S14 and S21, table S6).

Aedes sp. eggs will hatch at the time of the first flood (*e.g.* at time t when $S^P(t) - S^P(t - \Delta t) > 0$), Thus during a small time Δt, the variation in the number of mature eggs due to hatching can be modeled as:

$$O_M(t) - O_M(t - \Delta t) \approx$$
$$-\max\left[\overbrace{\rho_A(t)\left(\kappa^{\text{Aedes}} S^P(t) - \kappa^{\text{Aedes}} S^P(t - \Delta t)\right)}^{\text{Number of submerged eggs}}, 0\right] \quad [2]$$
$$[3]$$

i.e. if the water body is shrinking, no eggs will be submerged and thus no egg will hatch; leading to:

$$O_M(t) - O_M(t - \Delta t) = -\max\left[\frac{\left(S^P(t) - S^P(t - \Delta t)\right)}{S^P(t)}, 0\right] O_M(t) \quad [4]$$

where the superficial density of eggs at time t was estimated as $\rho_A(t) \approx O_M(t)/(\kappa^{\text{Aedes}} S^P(t))$. The continuous counterpart

of the above equation leads to:

$$\tau_O^{\text{Aedes}} = \max\left(\frac{1}{S^P(t)}\frac{\mathrm{d}S^P(t)}{\mathrm{d}t}, 0\right) \qquad [5]$$

where the term $\frac{\mathrm{d}S^P(t)}{\mathrm{d}t}$ represents the rate of change of the surface area of a water body.

Combined mosquito and livestock population model in the presence of infection. RVFV transmission in *Aedes* mosquitoes can be transovarial or horizontal while only horizontal transmission, mediated by biting infectious hosts, is possible for *Culex* sp. Both adult *Culex* sp. and *Aedes* sp. can become infected after feeding on infectious livestock I_L. More precisely, for *Culex* sp., the movement out from the susceptible categories, C_1 and C_2, are $\tilde\theta_{C1}^{Culex}C_1$ and $\tilde\theta_{C2}^{Culex}C_2$ respectively; out of these, $\lambda_{L\to C_1}C_1$ and $\lambda_{L\to C_2}C_2$ mosquitoes move to the exposed, flyer category, F_C^{Exp}. The remaining $(\tilde\theta_{C1}^{Culex} - \lambda_{L\to C_1})C_1$ and $(\tilde\theta_{C2}^{Culex} - \lambda_{L\to C_2})C_2$ move to the susceptible, flyer category, F_C. Similar argument apply to *Aedes* sp., but in this case, there is an additional infectious category for nulliparous mosquitoes, A_1^{Inf}, emerging out of infectious eggs due to transovarial transmission. The exposed categories then transit to the adult infectious categories (C_1^{Inf} and C_2^{Inf} for *Culex*, and A_1^{Inf} and A_2^{Inf} for *Aedes*) with rate ϵ_C and ϵ_A respectively. The exposed and infectious populations will lead to the exposed and infectious flyer populations (F_C^{Exp} and F_C^{Inf} for *Culex* sp., and F_A^{Exp} and F_A^{Inf} for *Aedes* sp.) followed by cyclic transitions to the corresponding exposed and infectious adult stages and back to the exposed and infectious flyer stages. Furthermore, infected *Aedes* sp. flyer (*i.e.* either exposed (F_A^{Exp}) or infectious (F_A^{Inf})), will deposit infectious eggs O_I^{Inf} which will turn into infectious larvae L_A^{Inf}, infectious pupae P_A^{Inf} infectious nulliparous adults A_1^{Inf}, etc. The explicit set of differential equations is presented in the SI Appendix, , S1 Text. Parameters are based on data presented in the literature (see (40, 42, 72) and references therein, tables S3, S4 and S5) and adapted to the Kenya situation (*e.g.* temperature (56), and water bodies (71)).

Stability analysis for seasonal systems: Floquet theory. Floquet analysis is a well-established tool suitable to study the stability of seasonal systems (77, 78). In the simplest scenarios, temperature and water bodies can be approximated by the periodic functions:

$$S^P(t) = S_m^P + S_A^P \cos\left(\omega_S t + \phi_S\right) \qquad [6]$$

$$T(t) = T_m + T_A \cos\left(\omega_T t + \phi_T\right) \qquad [7]$$

where ω_S and ω_T are the frequencies of oscillations in surface areas of water bodies and temperature, the terms S_m^P and T_m represent the mean surface area of water bodies and mean temperature during a period $2\pi/\omega_S$ and $2\pi/\omega_T$ respectively, S_A^P and T_A are the maximum amplitude in the oscillations and ϕ_S and ϕ_T are the respective phases. Then we ran the model, and calculated the corresponding Floquet multipliers, for a range of frequencies, mean surface area of water bodies and mean temperature to explore which of these parameters lead to stable solutions. More details are in the SI Appendix, , S1 Text.

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