Estimation of Rift Valley fever virus spillover to humans
during the Mayotte 2018-2019 epidemic

Raphaëlle Métras\textsuperscript{a,b,c} PhD, W John Edmunds\textsuperscript{d} PhD, Chouanibou Youssouffi\textsuperscript{e} BSc, Laure Dommergues\textsuperscript{f} DVM, Guillaume Fournié\textsuperscript{g} PhD, Anton Camacho\textsuperscript{d,h} PhD, Sebastian Funk\textsuperscript{d} PhD, Eric Cardinale\textsuperscript{a,i} PhD, Gilles Le Godais\textsuperscript{j} MSc, Soihibou Combo\textsuperscript{f} BSc, Laurent Filleul\textsuperscript{k} PhD, Hassan Youssouf\textsuperscript{k,*} PhD, Marion Subiros\textsuperscript{k,**} MSc.

*these authors share last authorship

\textsuperscript{a} CIRAD, UMR ASTRE, Campus International de Baillarguet, 34398 Montpellier, France
\textsuperscript{b} ASTRE, Univ Montpellier (I-MUSE), CIRAD, INRA, 34398 Montpellier, France
\textsuperscript{c} Inserm, Sorbonne Université, Institut Pierre Louis d’Épidémiologie et de Santé Publique (iPLesp), 27 rue de Chaligny, 75012 Paris, France.
\textsuperscript{d} Centre for the Mathematical Modelling of Infectious Diseases, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, Keppel Street WC1E 7HT, London, United Kingdom
\textsuperscript{e} GSD Mayotte-Coopérative Agricole des Eleveurs Mahorais, 97670 Coconi, Mayotte, France
\textsuperscript{f} La Coopération Agricole, 43 rue Sedaine, F-75538 Paris, France
\textsuperscript{g} Veterinary Epidemiology, Economics and Public Health group, Department of Pathobiology and Population Sciences, The Royal Veterinary College, Hatfield, United Kingdom
\textsuperscript{h} Epicentre, 14-34 avenue Jean Jaurès, 75019 Paris, France
\textsuperscript{i} CIRAD, UMR ASTRE, F-97490 Sainte Clotilde, La Réunion, France
\textsuperscript{j} Direction de l’Alimentation, de l’Agriculture et de la Forêt de Mayotte, Mamoudzou, France
\textsuperscript{k} Santé Publique France, Mamoudzou, Mayotte, France
Abstract

Background. Rift Valley fever (RVF) is an emerging, zoonotic, arboviral haemorrhagic fever threatening livestock and humans mainly in Africa. In the absence of a human vaccine, estimating the transmission potential of RVF virus from livestock to humans is key to assessing the impact of livestock disease control measures on preventing human disease.

Methods. We combined a unique RVF dataset, with livestock and human surveillance data of the 2018-2019 RVF epidemic in Mayotte, and used them in a mathematical model. Using Bayesian inference, we quantified the transmission amongst livestock and spillover to humans, and we assessed the impact of livestock vaccination on reducing human disease risk.

Findings. Vaccination scenarios indicate that early livestock vaccination (December 2018) would have reduced the human epidemic size by a third, whilst vaccinating one month later required using 50% more vaccine doses for a similar impact. In addition, the likelihood of virus re-emergence in the next rainy season (2019-2020) was estimated very low, with 55.8% (90 Credible Interval [27.1-59.5]) of the livestock population being immune in August 2019.

Interpretation. Human and livestock health surveillance, early detection, and timely vaccination in livestock are crucial to reducing disease risk in humans. We present the first study quantifying RVF virus spillover using livestock and human data, and use this quantitative information to inform on the impact of potential control programmes. This demonstrates the value of a One Health approach to surveillance and control of this emerging infectious disease. Funding. ARS Océan Indien, EAFRD, RITA Mayotte, VEEPED, Wellcome.
Introduction

Controlling zoonotic and vector-borne infections is complex, and requires getting an accurate understanding of pathogen transmission within animal populations, and pathogen spillover to humans, whilst accounting for environmental factors impacting on vectors.\textsuperscript{1,2} Rift Valley fever (RVF) is an emerging zoonotic arbovirosis and an haemorrhagic fever that is threatening animal and human health, mainly in Africa.\textsuperscript{3} Livestock (cattle, sheep and goats) are RVF virus amplifying hosts, acquiring infection through the bites of infectious mosquitoes (mainly \textit{Aedes} spp. and \textit{Culex} spp.).\textsuperscript{4} Humans acquire infection by direct contact with infectious animal tissues (upon abortions or animal slaughter), although vector transmission may also play a role.\textsuperscript{4,5} Since 2015, RVF has been listed as a priority emerging disease by the WHO R&D Blueprint\textsuperscript{6} and is today of global health concern,\textsuperscript{7} particularly as it has significantly expanded its geographical range over recent decades.\textsuperscript{5} Current disease control options for reducing disease risk in humans heavily rely on controlling virus transmission in animal populations. The impact of disease control measures in livestock on reducing RVF risk in humans has not yet been assessed, and doing so requires estimating key transmission parameters between livestock and from livestock to humans; using animal and human epidemiological data.

Mayotte, an island located in the South Western Indian Ocean region, reported a RVF epidemic in 2007-2008.\textsuperscript{8} In a previous paper, we used longitudinal livestock seroprevalence data to model RVF virus emergence in the livestock population, and we estimated that the likelihood of re-emergence was very low in a closed ecosystem (i.e. without the import of infectious animals). However, a few imported infectious animals would be sufficient to trigger another large epidemic, especially if neighbouring countries were affected and levels of herd immunity had declined due to livestock population turnover.\textsuperscript{9} About ten years later, in 2018, RVF outbreaks were reported in several East African countries (e.g. Kenya, South Sudan, Uganda, Rwanda).\textsuperscript{10,11} In Mayotte, between November 2018 and August 2019, a total
of 143 human cases (RVF virus RT-PCR confirmed) were reported (figure 1). The Veterinary Services of Mayotte, the regional health authorities (Agence de Santé Océan Indien) and the French Public Health Agency (Santé Publique France) did further epidemiological investigations to track the level of virus transmission in the animal population and study the possible route of human exposure to RVF virus. These investigations produced a uniquely well documented RVF epidemic, with both human and livestock datasets, including incidence and prevalence data.

We present these data and use them to extend the mathematical model previously developed to study RVF virus transmission in the livestock population in Mayotte, by explicitly modelling the human population. We fit this new mathematical model to both livestock and human epidemiological datasets from the 2018-2019 epidemic, allowing for the first time (i) to estimate the probability of RVF virus transmission to humans (virus spillover), (ii) to estimate the likelihood of another epidemic, and (iii) to assess the impact of different vaccination strategies in livestock on the disease risk reduction in humans.

Methods

Data: the course of the epidemic in both humans and livestock

The first human case, defined as a patient showing dengue-like symptoms and testing positive to RVF virus RT-PCR was reported at the end of November 2018. The number of reported cases rose quickly after the start of the rainy season (figure 1). The epidemic peaked around week 7 of 2019 (February 11-17, 2019), with 18 confirmed cases. Between November 2018 and August 2019, a total of 143 confirmed RVF human cases were reported. From these 143 human cases, 127 were investigated and 16 were lost to follow-up. All investigated cases were indigenous, most of them were male (male/female ratio=3), with a median age of 41 years-old [age range : 4-75] (13% were under 20, 80% were between 20 and 65 years-old, and
7% were over 65). About two-third of investigated cases (68%, n=86) reported having regular direct contact with livestock, whilst 32% (n= 41) reported no previous contact with animals. Symptoms were available for 98 cases, including fever, headache, arthralgia, asthenia, myalgia, nausea and vomiting, and retro-orbital pain. In addition, between July 2018 and June 2019, a total of 1169 livestock sera, collected as part as the annual surveillance campaign, were tested against RVF IgG (ID Screen RVF Competition ELISA, IDVet, Grabels, France). RVF IgG antibodies can be detected in infected animals from about a week post-infection, and up to several years.® Date of birth was available for 493 of these sampled animals, and to follow the emergence of the virus in the livestock population, we plotted quarterly age-stratified RVF IgG prevalence for the period July 2018 to June 2019 (figure 2A-D). In the third quarter of 2018 (July - September 2018), that is before the report of the first human case, the oldest animals were seropositive (figure 2A) probably from the previous epidemic.® The IgG prevalence increased in all age groups during the first quarter (January-March 2019, figure 2C) and second quarter (April-June 2019, figure 2D) of 2019, coincident with the reported cases in humans. Moreover, sera from illegally imported livestock seized by the Veterinary Services between June and August 2018 tested positive to RVF IgM (indicative of recent infections) (table 1). Finally, ongoing phylogenetic analyses on human-derived samples suggest that the incriminated RVF virus lineage may belong to the Kenya-2 clade, and is closely related to the strains from recent outbreaks in Eastern Africa (Cardinale, pers comm).

Model assumptions
We used these human and livestock data to develop our mathematical model. The study period ranged from the first week of July 2018 (week 27, July 2nd-9th) until the first week of August 2019 (week 31, July 29th- August 4th 2019), capturing the period between the
assumed importing time-window of infectious animals and the last reported human case. Based on the data from illegally imported livestock, we assumed that RVF virus was imported in Mayotte in July 2018, at which time most indigenous livestock were susceptible. Throughout the epidemic, we assumed humans were infected by direct contact with infectious livestock.

**Model structure**

The SEIR mathematical model of emergence previously developed for RVF in the livestock population of Mayotte was adapted to the current epidemiological context. A discrete-time deterministic framework was used, with a daily time step. For full details on the model in livestock, see Metras and colleagues. As a reminder, transmission of RVF virus amongst livestock ($\beta_{\text{livestock-livestock}}(t)$), was assumed to be vector-borne and modelled as a function of monthly NDVI (Normalized Difference Vegetation Index) values as a proxy for vector abundance. Here we used rainfall data instead of NDVI as the study period, the time step and the human epidemic curve available for fitting had a smaller time resolution (Appendix p2, equations S1a-S1c). To this livestock model, we added a module simulating RVF virus spillover from livestock into the human population, that is, the transmission of RVF virus from livestock to humans. In this model (noted Model 1), we assumed that humans acquired infection by direct contact with livestock (figure S1). Humans were Susceptible ($S_h$), became infected by direct contact ($E_{hc}$) with infectious livestock; after which they were successively infectious ($I_{hc}$) and immune ($R_h$). The corresponding model equations, transmission parameter $\beta_{\text{livestock-human}}$ and force of infection by direct contact with livestock $\lambda_{\text{contact}}(t)$ are presented in the supplementary appendix (Appendix p2, equations S2a-S2e).
Model parameterization and fitting

Model parameters related to the natural history of infection (in animals and humans), and to the structure of livestock and human populations were fixed (appendix p4, table S1). Animals from all age-groups were assumed susceptibles at time $t_0$, except the age-groups 9 and 10, for which the proportion of immune at $t_0$ were 5% and 20.5%, respectively (as per the 2017-2018 IgG seroprevalence campaign). The reporting fraction of human cases was set to $\rho=1.9\%$, as a post-epidemic serological study in humans, conducted in 2011 in Mayotte, estimated that 3.5% (95% CI [2.6 - 4.8]) of the human population was RVF IgG-positive.$^{14}$ Assuming a population size of 212,645 inhabitants in 2012,$^{15}$ this corresponds on average to 7,442 persons being seropositive. Assuming that the past epidemic size is similar to the present one, and based on 143 cases currently reported, gives a reporting fraction of 1.9% (95% CI [1.4 – 2.5]). Finally, we seeded the model with 10 infectious animals at $t_0$ ($t_0=$Monday 2nd July, 2018), representing the infectious imports.

Parameters related to rainfall-dependent and constant viral transmission (appendix p4, model 1, table S1) were estimated by fitting the model to data. Parameter estimation was done by fitting simultaneously the (i) quarterly age-stratified simulated proportion of immune livestock ($p_{a,q}$) to quarterly RVF IgG prevalence (appendix p5, equation S5a, and figure 2AD); and (ii) the simulated weekly number of reported incident cases in humans (appendix p5, equation S6c) to the weekly number of reported cases (figure 1, all cases). For fitting, we sampled from the posterior distributions of three parameters, $\theta_1 = \{A, B, \beta_{livestock-human-c}\}$ (appendix p6) using a Monte Carlo Markov Chain Metropolis-Hastings (MCMC-MH) algorithm.$^{16}$ For details on parameter estimation and model fitting, see appendix p5-6.

Finally, rainfall data were downloaded from Meteofrance website, as cumulated rainfall over 10-day periods.$^{13}$ Daily rainfall, used as input data in the model, was calculated by dividing these values by ten over each 10-day period.
Forecasting and vaccination scenarios

We did projections for six scenarios (table 2). For all scenarios, we simulated 2,500 stochastic trajectories by sampling randomly from the posterior distributions of the estimated parameters, and we seeded the model with 10 infectious ($I_{lv}$) livestock. Scenario 1 aimed at estimating the likelihood of virus re-emergence, without disease control intervention, in the following rainy season, that is 2019-2020, in a closed ecosystem, using the same rainfall values as in the 2018-2019 rainy season. Scenarios 2-6 aimed at assessing the impact that different livestock vaccination strategies could have had on the number of human cases in the past epidemic (2018-2019). We assumed the use of a single-dose highly immunogenic vaccine (90% vaccine efficacy), and a 14-days lag between vaccination and build-up of immunity. Figures of vaccination campaigns in Mayotte in 2017 (vaccination for other livestock diseases conducted on the island), showed that about 3,000 vaccine doses are routinely administered to livestock over a year by the local veterinarians (Data CoopADEM, not shown). Scenario 2 tested the impact of administrating all these 3,000 doses in one month, in December 2018, immediately after the report of the first human case (joint animal-human alert date for response), corresponding to the current vaccinating capacity in Mayotte in an emergency setting. Scenario 3 assumed that all 3,000 doses were administered in January 2019, one month following the report of first human case, allowing extra time for organising the vaccination campaign. Scenario 4-6 assumed an extra-vaccine supply and an emergency mass vaccination, allowing 6,000 doses to be administered in December 2018 (Scenario 4), 6,000 doses to be administered in January 2019 (Scenario 5), and 9,000 doses to be administered in January 2019 (Scenario 6).

Sensitivity analysis

To test for the possibility of a viral transmission from livestock to humans by direct contact and by vector transmission, and to assess the impact of rainfall on transmission, we also
developed two further models and compared them (Model 2 and Model 3, table S2). Details on models equations, parameters, fitting methods and model comparison are presented in the appendix p3-7.

**Ethics statement**

The livestock data were collected under the Mayotte disease surveillance system (Système d’Epidémiosurveillance Animale à Mayotte, SESAM) with the approval of the Direction of Agriculture, Food and Forestry (DAAF) of Mayotte. For human data, according to French law, only “research involving a human being” (research defined by article L. 1121–1 and article R. 1121–1 of the Code de la santé publique) are compelled to receive the approval of ethics committee. This study was based on anonymous data collected from health professionals for public health purposes relating to the health surveillance mission entrusted to Santé publique France by the French Law (article L. 1413-1 code de la santé publique). Therefore, the study did not meet the criteria for qualifying a study “research involving a human being” and did not require the approval of an ethics committee. Furthermore, as the data were anonymous, it did not require an authorization of the French data protection authority (Commission Nationale informatique et libertés).

**Role of the funding sources**

The funding sources have no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.
Results

The median number of predicted human reported cases was 140 (90% Credible Interval CrI [9 - 265], table 2 and figure 3A) showing good agreement with the observed confirmed cases (143 cases, figure 3A), and the livestock IgG prevalence data (figure 2AD). The epidemic started in November 2018, shortly after the rainy season started. The epidemic peaked in livestock during the 5th week of 2019 (week 31 of the model, January 28 - February 3, 2019) and two weeks later in humans (week 33 of the model, February 11-17, 2019) (figure 3B and table 2). The total median number of predicted human cases was 7,362 (90%CrI [458 – 13,962]), corresponding to 3·0% (90%CrI [1·2 - 3·6]) of the total human population (table 2).

For livestock, the total number of animals affected at the end of the epidemic were estimated to 18,801 (90%CrI [1,250 - 35,572]), corresponding to 55·8% (90%CrI [27·1 - 59·5]) of the total livestock population (figure 3C and table 2).

The timing-varying reproductive number $R_s(t)$ in the livestock population was a function of rainfall and varied along the study period (figure 3D). Its maximum value (median $R_s(t)$=2·24, 90%CrI [1·77 – 3·10]) was reached on the first week of 2019 (December 31, 2018 - January 6th, 2019, 87·4 mm of cumulated rain on that week), that is four and six weeks prior to the peaks in livestock and humans, respectively. Finally, the constant transmission rate from livestock to humans was estimated at 2·2 per 10 million inhabitants per day (95%CrI [1·8 – 2·7]) (appendix p8, table S3).

The probabilistic forecasts showed that RVF re-emergence in the next rainy season (2019-2020) was very unlikely (figure 2A). Figure 4AD presents the results of the impact of the different livestock vaccination strategies on the number of human reported incident cases (figure 4AB) and livestock incident cases (figure 4CD). The implementation of massive vaccination campaign immediately after the first human case (table 2, Scenario 4, i.e. 6,000 doses in December 2018) allowed reducing the number of human cases reported by a third.
(median = 94 cases), while waiting one more month would have required 50% more vaccine
doses for a similar impact (figure 4AD and table 2, Scenario 6, i.e. 9,000 doses in January
2019, n=93 cases). The two alternative models tested as sensitivity analysis (Model 2 and 3)
did not fit the data as well as Model 1 (appendix p7, figure S2AB, and table S2). For Model 2,
the spillover to humans via direct contact was slightly lower than in Model 1, estimated at 1.3
per 10 million inhabitants per day (95% CrI [2.1–1.9]) (appendix p8, table S3). In this model,
the maximum $R_s(t)$ values in livestock was $R_s(t)= 2.48$ (90% CrI [1.96 - 3.46]), and the
intensity of the vector transmission from livestock to humans represented 0.6% (95% CrI
[0.12 – 2.1]) of the between livestock vector transmission (scaling factor $X$, appendix p8,
table S3).

Discussion

This paper presents a dataset of a large RVF epidemic, combining prospectively collected
livestock and human data, which represents a reference case study for RVF. Testing of human
cases of dengue-like syndrome with RVF RT-PCR has been systematically performed in
Mayotte for the last ten years (since 2008), giving confidence that RVF had been absent from
the Island for a decade, and that the shape of the epidemic curve accurately reflected its actual
timing. This was cross-validated by the observed changes in the seroprevalence in livestock,
exhibiting a clear pattern of viral emergence. Finally, the routine IgM testing of illegally
imported livestock provided an estimate of the likely time-window of virus importation,
which also coincided with the timing of RVF outbreaks on the East African mainland.11

We used these data to fit a mathematical model to quantify transmission amongst livestock
and spillover to the human population, to estimate the likelihood of another emergence in the
following rainy season (2019-2020), and to assess the impact of livestock vaccination on
preventing disease risk in humans. At the end of the modelled epidemic wave, in August
2019, the proportion of immune livestock was estimated at 55·8 % (90%CrI [27·1 - 59·5]), and the likelihood of RVF re-emergence in Mayotte in the 2019-2020 rainy season was very low. We also demonstrated that reactive vaccination (6,000 animals vaccinated in December 2018) would have reduced the number of human cases by a third, while 50 % more vaccine doses would have been necessary a month later for a similar impact. This highlights that animal vaccination can prevent human cases, as well as cases in livestock, but that early detection and rapid vaccination are critical to RVF control at the early stage of the epidemic.

Rainfall is a known driver for RVF virus transmission, and was used as a proxy for vector abundance. Temperature above 26ºC may also drive RVF virus transmission. The temperatures of Mayotte varying annually between 25ºC and 35ºC, we therefore assumed that temperature would not be a driver for transmission in this setting. In areas with cooler climates, temperature should be explicitly modelled. The highest estimated Rs(t) value was 2·24 (90%CrI [1·77 – 3·10]), in line with previous estimations of R₀. Finally, previous models parameterised the transmission parameter from livestock to humans as a fixed parameter at 1·7 per 10 thousand persons per day. For the first time, our model estimated that value, which was lower, at 2·2 per 10 million persons per day (95%CrI [1.8 – 2·7]). This can be used as benchmark for future modelling work.

RVF human cases without previous contact with animals or animal products have been reported in other settings, although this fraction had not been documented during an epidemic. Here, the epidemiological investigations documented the fraction of cases that had no contact with animals, and were therefore probably infected via mosquito bite. Regarding livestock data, sera were tested as part of the national surveillance campaign, and some samples were taken in areas reporting human cases. This may have led to an over-estimate the proportion of IgG positive animals. However, most animal sampling was conducted from January 2019 onwards, when RVF virus had already spread across the whole island.
A limitation of the model related to the parameterization of the reporting rate in humans, used as an input value. For this, we used past data, assuming the 2007-2008 wave was of similar size to the 2018-2019 epidemic. Whilst there is no human data to support this assumption, our previous work estimated an overall post-epidemic livestock prevalence at about 50%, which is in line with our current estimates. Further data collection estimating human post-epidemic prevalence would allow an accurate estimation of this reporting rate. In addition, the limited total number of human reported cases led to wide confidence intervals for the forecasts.

Collecting more epidemic data at a smaller spatio-temporal resolution would have also allowed spatial stratification, and testing for finer vaccination protocols. Finally, as in our previous model, we assumed homogeneous mixing. However, Mayotte is a small island (374km²), the ecosystem shows limited spatial variations, livestock production systems are extensive with animals raised outdoor, and therefore potentially similarly exposed to RVF mosquito vectors.

As long as no vaccination in humans is available, disease surveillance in animals, contingency planning, and the timely implementation of livestock vaccination, are key for reducing human disease risk. During this epidemic, livestock were not vaccinated due to a lack of vaccine supply, and limited human resources, and the vaccination scenarios tested would require emergency funds and vaccine doses.

This is a uniquely detailed investigation into an outbreak of an emerging arbovirus, combining animal and human data, with a mathematical model for RVF. This work represents a collaboration between public health agency, animal health surveillance network, farmers’ association, and researchers, from the beginning of the epidemic, and conducted in real-time, as the epidemic unfolded. Delays in getting serological data were inherent to climatic conditions (storms) and field work constraints in remote areas. Nevertheless, we addressed in
practice the challenges of a One Health approach,\textsuperscript{30} and this work demonstrates its value to surveillance and control of zoonotic emerging infectious diseases.

**Acknowledgements**

The authors wish to thank the Agence de Santé océan Indien that has participated in collecting human cases data, the laboratory of Centre Hospitalier de Mayotte which has performed the virological analyses on human samples, the animal SESAM surveillance system, the CoopADEM (Coopérative agricole des éleveurs mahorais), the Cirad-CYROI, the Veterinary Services, and the LVAD (Laboratoire Vétérinaire d’Analyses Départemental de Mayotte) for the data collection and the serological analyses on livestock samples. Finally, we thank Harold Noël (MD) from Santé publique France for facilitating human data access in the early stage of the epidemic.

**Declaration of interests**

The authors declare no conflict of interest.

**Funding sources**

RVF RT-PCR were conducted as part of the surveillance system on dengue-like syndrome since 2008, funded by Agence de Santé océan Indien. The animal sampling and analyses were funded by EAFRD (European Agricultural Fund for Rural Development) and RITA (Réseau d’Innovation et de Transfert Agricole) Mayotte. WJE and AC were funded by the Department of Health and Social Care using UK Aid funding managed by the NIHR (VEEPED: PR-OD-1017-20007). The views expressed in this publication are those of the authors and not necessarily those of the Department of Health and Social Care. SF was funded by a Wellcome Senior Research Fellowship (210758/Z/18/Z).
Contributions

The corresponding author (RM) had access to all the data in the study and had final responsibility for the decision to submit for publication. RM, WJE, LD, GF, YH, MS conceptualized and designed the study. CY, LD, SC, YH, MS collated the data and did data management. RM, GF performed the analyses. RM, WJE, CY, LD, GF, AC, SF, GLG, CS, EC, LF, YH, MS interpreted and discussed the data and results. RM was responsible for drafting the manuscript. All authors reviewed and approved the final manuscript.

References

1. Woolhouse MEJ, Dye C. Preface. Philos Trans Roy Soc London Ser B 2001; 356: 981–982.

2. Jones BA, Grace D, Kock R, et al. Zoonosis emergence linked to agricultural intensification and environmental change. Proc Natl Acad Sci U S A 2013; 110:8399-404.

3. Clark MHA, Warimwe GM, Di Nardo A, Lyons NA, Gubbins S. Systematic literature review of Rift Valley fever virus seroprevalence in livestock, wildlife and humans in Africa from 1968 to 2016. PLoS Negl Trop Dis 2018;12:e0006627. doi:10.1371/journal.pntd.0006627

4. Bird BH, Ksiazek TG, Nichol ST and MacLachlan NJ. Rift Valley fever virus. J Am Vet Med Assoc 2009;234:883–893.

5. Nanyingi MO, Munyua P, Kiama SG, et al. A systematic review of Rift Valley Fever epidemiology 1931–2014. Infect Ecol Epidemiol 2015; 5: 10.3402/iee.v5.28024
6. World Health Organization. 2018. Epidemic and pandemic-prone diseases, List of Blueprint priority diseases. Available at http://www.emro.who.int/fr/pandemic-epidemic-diseases/news/list-of-blueprint-priority-diseases.html Accessed on Nov 26, 2019.

7. Hatchett R and Lurie N. Outbreak responses as an essential component of vaccine development. *Lancet Infect Dis* 2019;19:e399-e403. doi:10.1016/S1473-3099(19)30305-6

8. Métras R, Cavalerie L, Dommergues L, et al. The Epidemiology of Rift Valley Fever in Mayotte: Insights and Perspectives from 11 Years of Data. *PLoS Negl Trop Dis* 2016;10:e0004783. https://doi.org/10.1371/journal.pntd.0004783

9. Métras R, Fournié G, Dommergues L, et al. Drivers for Rift Valley fever emergence in Mayotte: A Bayesian modelling approach. *PLoS Negl Trop Dis* 2017;11:e0005767. https://doi.org/10.1371/journal.pntd.0005767

10. ProMED. Rift Valley fever - Kenya (02): (Wajir). Published Date: 2018-06-09. Archive Number: 20180609.5847216. Accessed on Dec 5th 2019.

11. Food and Agriculture Organization of the United Nations. EMPRES-i. Global Animal Disease Information System. Available at: http://empres-i.fao.org/eipws3g/ . Accessed on Dec 11th, 2019.
12. Bird BH, Bawiec DA, Ksiazek TG, Shoemaker TR, Nichol ST. Highly sensitive and broadly reactive quantitative reverse transcription-PCR assay for high-throughput detection of Rift Valley fever virus. *J Clin Microbiol* 2007;45:3506–3513. doi:10.1128/JCM.00936-07

13. Météo France. 2019. Données décadaires agrométéorologiques. Available at: https://donneespubliques.meteofrance.fr/?fond=produit&id_produit=113&id_rubrique=37 Accessed on Sept 23, 2019.

14. Lernout T, Cardinale E, Jego M, et al. Rift Valley Fever in Humans and Animals in Mayotte, an Endemic Situation? *PLoS ONE* 2013; 8: e74192. https://doi.org/10.1371/journal.pone.0074192

15. Institut National de la statistique et des études économiques (Insee). Habitants a Mayotte. 2017 Available at: https://www.insee.fr/fr/statistiques/3286558#documentation, Accessed on Oct 5, 2019.

16. Camacho A and Funk S. fitR: Tool box for fitting dynamic infectious disease models to time series. R package version 0.1.

17. Dungu B, Lubisi BA, Ikegami T. Rift Valley fever vaccines: current and future needs. *Curr Opin Virol* 2018;29:8-15. doi: 10.1016/j.coviro.2018.02.001

18. Sang R, Lutomiah J, Said M, et al. Effects of Irrigation and Rainfall on the Population Dynamics of Rift Valley Fever and Other Arbovirus Mosquito Vectors in the Epidemic-Prone Tana River County, Kenya. *J Med Entomol* 2017;54:460–470. doi:10.1093/jme/tjw206
19. Turell M J, Rossi CA and Bailey CL. Effect of extrinsic incubation temperature on the ability of Aedes taeniorhynchus and Culex pipiens to transmit Rift Valley fever virus. *Am J Trop Med Hyg* 1985;34:1211–1218.

20. Brubaker JF and Turell MJ. Effect of environmental temperature on the susceptibility of Culex pipiens (Diptera: Culicidae) to Rift Valley fever virus. *J Med Entomol* 1998;35:918–921.

21. Lo Iacono G, Cunningham AA, Bett B, Grace D, Redding DW, Wood JLN. Environmental limits of Rift Valley fever revealed using ecoepidemiological mechanistic models. *Proc Natl Acad Sci U S A* 2018;115:E7448–E7456. doi:10.1073/pnas.1803264115

22. Esser HJ, Mögling R, Cleton NB, et al. Risk factors associated with sustained circulation of six zoonotic arboviruses: a systematic review for selection of surveillance sites in non-endemic areas. *Parasit Vectors* 2019;12:265. doi:10.1186/s13071-019-3515-7

23. Barker CM, Niu T, Reisen WK, Hartley DM. Data-Driven Modeling to Assess Receptivity for Rift Valley Fever Virus. *PLoS Negl Trop Dis* 2013; 7: e2515. https://doi.org/10.1371/journal.pntd.0002515

24. Xue L, Scott MH, Cohnstaedt LW and Scoglio C. A network-based meta-population approach to model Rift Valley fever epidemics. *J Theor Biol* 2012;306:129–144. doi: 10.1016/j.jtbi.2012.04.029
25. Danzetta ML, Bruno R, Sauro F, Savini F and Calistri P. Rift Valley fever transmission dynamics described by compartmental models. *Prev Vet Med* 2010;134:197–210. [https://doi.org/10.1016/j.prevetmed.2016.09.007](https://doi.org/10.1016/j.prevetmed.2016.09.007)

26. Mpeshe SC, Haario H and Tchuenche JM. A Mathematical Model of Rift Valley Fever with Human Host. *Acta Biotheor* 2011; 59: 231. [https://doi.org/10.1007/s10441-011-9132-2](https://doi.org/10.1007/s10441-011-9132-2)

27. Lugoye J, Wairimu J, Alphonce CB, Ronoh M. Modeling Rift Valley fever with treatment and trapping control strategies. *Appl Math* 2016;7:556-568

28. Archer BN, Thomas J, Weyer J, et al. Epidemiologic Investigations into Outbreaks of Rift Valley Fever in Humans, South Africa, 2008-2011. *Emerg Infect Dis* 2013;19:1918–1925. doi:10.3201/eid1912.121527

29. Shoemaker TR, Nyakarahuka L, Balinandi S, et al. First Laboratory-Confirmed Outbreak of Human and Animal Rift Valley Fever Virus in Uganda in 48 Years. *Am J Trop Med Hyg* 2019;100:659–671. doi:10.4269/ajtmh.18-0732

30. Scoones I, Jones K, Lo Iacono G, Redding DW, Wilkinson A, Wood JLN. Integrative modelling for One Health: pattern, process and participation. *Philos Trans R Soc Lond B Biol Sci* 2017;372:20160164. doi:10.1098/rstb.2016.0164
Figures

Figure 1. Weekly number of reported human cases and average daily rainfall pattern (mm). Between November 2018 and July 2019, 143 cases were reported. A total of 86 cases reported a direct exposure to livestock or their fluids (red), 41 did not report any direct exposure to livestock (green), and 16 were lost to follow-up (grey).
Figure 2AD. Quarterly age-stratified RVF IgG seroprevalence in livestock. The black dots and vertical black lines represent the observed age-group average IgG prevalence, and their 95%CI. Median (solid blue line), boundaries of the 90% CrI (dashed blue lines), and the interquartile range (dotted blue lines) of the predicted values. (A) for the trimester July-September 2018, (B) October – December 2018, (C) January – March 2019, and (D) April – June 2019.
Figure 3AD. Model results. (A) Weekly reported incident human cases. Observed data (red dots), predicted median (red solid line), interquartile range (dashed lines) and 90% CrI (red envelope). (B) Predicted (reported and unreported) number of infectious livestock (blue) and humans (red). (C) Median (solid lines) and 90% CrI envelopes of the predicted proportion of Susceptible (green) and Immune (black) livestock over the course of the epidemic. (D) Value of $R_s(t)$ over the course of the epidemic, and 90% CrI. In (A), (B) and (C), the vertical blue and red vertical lines correspond to the predicted epidemic peaks in livestock and humans, respectively. The vertical black line corresponds to the end of August 2019 (end of the fitting period).
Figure 4AD. Comparison of the vaccination strategies versus no intervention. (A) Median weekly number of incident human cases and (B) Predicted number of human reported cases. (C) Median weekly number of incident infected livestock and (D) Predicted number of infected livestock. (A) and (C) present the scenario with no intervention (red solid line, Scenario 1), the vaccinations in December 2008 (the black solid line represents the 3,000 doses, and the dashed black line the 6,000 doses), and in January 2019 (the blue solid line represents the 3,000 doses, the dashed blue line the 6,000 doses; and the dotted blue line the 9,000 doses scenario).
Table 1. Number of illegally imported livestock seized by the Veterinary Services and positive to RVF IgM, between May and October 2018 (Source: Mayotte Veterinary Services)

| Month        | No. of IgM positive | No. animals seized | Proportion of IgM positive [95 % CI] |
|--------------|---------------------|--------------------|-------------------------------------|
| May 2018     | 0                   | 8                  | 0 % [0-40]                           |
| June 2018    | 10                  | 31                 | 32% [17-51]                          |
| August 2018  | 2                   | 18                 | 11% [2-36]                           |
| September 2018 | 0                 | 1                  | 0 % [0-90]                           |
| October 2018 | 0                   | 5                  | 0 % [0-54]                           |
| Scenario number | Scenario 1 | Scenario 2 (2.1) | Scenario 3 (2.2) | Scenario 4 (2.4) | Scenario 5 (2.3) | Scenario 6 (2.5) |
|-----------------|------------|-------------------|------------------|------------------|------------------|------------------|
| **Assumptions** | No intervention | 3,000 doses, Dec 2018 | 6,000 doses, Jan 2019 | 6,000 doses, Dec 2018 | 3,000 doses, Jan 2019 | 6,000 doses, Jan 2019 |
| **Epidemic size** | | | | | | |
| Total human cases | 7,362 [458-13,962] | 6,088 [542-11,564] | 6,410 [0-12,074] | 4,931 [28-9,240] | 5,552 [317-10,611] | 4,895 [135-9,122] |
| Human reported cases | 140 [9-265] | 116 [10-220] | 122 [0-230] | 94 [1-176] | 105 [6-202] | 93 [3-173] |
| Total livestock cases | 18,801 [13892-32,045] | 15,650 [1519-29,387] | 16,459 [10-30,890] | 12,586 [1677-23,276] | 14,182 [871-23,045] | 12,540 [389-23,045] |
| Human prevalence | 3·0·3·6-3·2·7 | 2·7·0·3·0-2·0·2·6 | 2·3·0·2·2-1·0·2·2 | 2·3·0·2·2-1·0·2·2 | 2·3·0·2·2-1·0·2·2 | 2·3·0·2·2-1·0·2·2 |
| Livestock prevalence | 458·4·2·3·9-458·4·2·3·9 | 458·4·2·3·9-458·4·2·3·9 | 458·4·2·3·9-458·4·2·3·9 | 458·4·2·3·9-458·4·2·3·9 | 458·4·2·3·9-458·4·2·3·9 | 458·4·2·3·9-458·4·2·3·9 |
| **Timing epidemic peaks** | | | | | | |
| Peak in humans | Week 33 | Week 33 | Week 33 | Week 32 | Week 32 | Week 32 |
| Peak in livestock | Week 33 | Week 33 | Week 33 | Week 31 | Week 31 | Week 31 |
| Post-epidemic size | | | | | | |
| No intervention | | | | | | |
| Scenario I | | | | | | |
| Scenario II (model 1) | | | | | | |