Supplementary Information for:

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

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Supplementary Information Text

Mathematical model: equations, parameter estimation, fitting and vaccination scenarios

SI Methods

The schematic diagram of the model is presented in Fig. 2 (main text), and the assumptions on viral transmission are presented in Table S1.

Model in livestock

The livestock population was stratified into 10 yearly age-groups (noted a, a ϵ [1,10]), as in Metras *et al.* 2017 (1). The model equations are presented in Eq. S1a-S1m. The force of infection of RVF virus between livestock *(λL-L(t))* (Eq. S2a) was assumed to be vector-borne and modelled as an exponential function of rainfall (2). Rainfall was used as a proxy for vector abundance, and varying over time (Eq. S2b and S2c). Indexing the state variables by yearly age-group *a*, and time *t*, the model in livestock is expressed as follows:

For $≤ 12$ months-old animals (i.e. age group a=1):

$$
S_{1,t+1} = (1 - \lambda_{L-L,t})(1 - \delta) \alpha S_{1,t} + b_t
$$
 (Eq. S1a)

$$
E_{1,t+1} = (1 - \delta)(1 - v_L)\alpha E_{1,t} + \lambda_{L-L,t}(1 - \delta)\alpha S_{1,t}
$$
 (Eq. S1b)

$$
I_{1,t+1} = (1 - \delta)(1 - r_L)\alpha I_{1,t} + (1 - \delta)v_L \alpha E_{1,t}
$$
 (Eq. S1c)

$$
R_{1,t+1} = (1 - \delta) \alpha R_{1,t} + (1 - \delta) r_L \alpha I_{1,t}
$$
 (Eq. S1d)

For > 12 months-old to \leq 108 months-old animals (i.e. age groups a ϵ [2–9]):

$$
S_{a,t+1} = (1 - \lambda_{L-L,t})(1 - \delta) \alpha S_{a,t} + (1 - \lambda_{L-L,t}) \delta \alpha S_{a-1,t}
$$
 (Eq. S1e)

$$
E_{a,t+1} = (1 - \delta) \left(1 - v_L\right) \alpha E_{a,t} + \lambda_{L-L,t} \alpha_a S_{a,t} + \lambda_{L-L,t} \alpha \delta S_{a-1,t}
$$
 (Eq. S1f)

$$
I_{a,t+1} = (1 - \delta)(1 - r_L)\alpha I_{a,t} + (1 - \delta)v_L\alpha E_{a,t} + \delta\alpha E_{a-1,t}
$$
 (Eq. S1g)

$$
R_{a,t+1} = (1 - \delta) \alpha R_{a,t} + (1 - \delta) r_L \alpha I_{a,t} + \delta \alpha I_{a-1,t} + \delta \alpha R_{a-1,t}
$$
 (Eq. S1h)

For > 108 months-old animals (i.e. age group *a* = 10):

$$
S_{10,t+1} = (1 - \lambda_{L-L,t}) \alpha_{10} S_{10,t} + (1 - \lambda_{L-L,t}) \alpha \delta S_{9,t}
$$
 (Eq. S1)

$$
E_{10,t+1} = (1 - \delta)(1 - v_L)\alpha E_{10,t} + \lambda_{L-L,t}\alpha_{10}S_{10,t} + \lambda_{L-L}\alpha\delta S_{9,t}
$$
 (Eq. S1i)

$$
I_{10,t+1} = (1 - \delta)(1 - r_L)\alpha I_{10,t} + (1 - \delta)v_L \alpha E_{10,t} + \delta \alpha E_{9,t}
$$
 (Eq. S1k)

$$
R_{10,t+1} = (1 - \delta) \alpha R_{10,t} + (1 - \delta) r_L \alpha I_{10,t} + \delta \alpha I_{9,t} + \delta \alpha R_{9,t}
$$
 (Eq. S11)

With:

$$
b_t = (1 - \alpha) \sum_{a=1}^{10} \left(S_{a,t} + E_{a,t} + I_{a,t} + R_{a,t} \right)
$$
 (Eq. S1m)

The force of infection amongst livestock was defined as:

$$
\lambda_{L-L,t} = 1 - \exp\left(-\beta_{L-L,t} \sum_{a=1}^{10} I_{a,t}\right)
$$
 (Eq. S2a)

With

$$
\beta_{L-L,t} = \frac{R_{s,t}}{N_L D_L} \tag{Eq. S2b}
$$

and

$$
R_{s,t} = \exp\left(A \; Rainfall_{t-LAG} + B\right) \tag{Eq. S2c}
$$

Where *Ia,t* is the number of infectious livestock in age-group *a*, at time *t*. *βL−^L ,t* is the rate of virus transmission between livestock, $R_{s,t}$ is the seasonal reproductive number at time *t*, N_L the total livestock population size, D_L the duration of infectiousness in livestock, Rainfall_{t-LAG} the value of rainfall 14 days (*LAG*=14 days) prior to time *t,* and *A* and *B*, the multiplying and scaling factors of the exponential function linking $R_{s,t}$ to rainfall. A and B are estimated by fitting the model to data (see paragraph on model fitting). The formulation of $R_{s,t}$ does not take account for the mortality of infected animals, as the mortality rates were much lower than the rates at which infected animals became infectious and infectious animals recovered from infection (1). Finally, as a base case, we allowed for a 14-days lag between rainfall and the presence of vectors (3,4), and ran also the model with a 21-days lag ('21-days lag case', Table S3).

We define $R_{e,t}$, the effective reproductive number, varying over time, as a function of $R_{s,t}$ multiplied by the proportion of susceptible animals at time *t* :

$$
R_{e,t} = R_{s,t} \sum_{a=1}^{10} S_{a,t} / N_L
$$
 (Eq. S2d)

Modelling virus spillover to humans

We added the human compartment to study RVF virus spillover, that is, the transmission of RVF virus from livestock to humans (Fig. 2, Table S1). The human population was divided into two groups: 'farming' and 'non-farming'.

In the farming group, susceptible humans S_{HF} were assumed to get infected E_{HF} by direct $\mathsf{contact}$ with animals and their tissues at a constant rate $\beta^{\mathsf{C}}_{{L-H}}$ and by the vector-mediated route at a time-varying rate $\pmb{\beta}^V_{L-H,t}$, before becoming successively infectious I_{HF} and immune R_{HF} . In the non-farming group, susceptible humans, S_{HNF} , acquired infection E_{HNF} only via the vectormediated route, at a time-varying rate $\beta^V_{L^-H,t}$, then became infectious I_{HNF} and immune R_{HNF} .

In the 'farming' group, the model is expressed as follows (Eq. S3a-S3f):

$$
S_{HF,t+1} = \left(1 - \lambda_{F,t}\right) S_{HF,t} \tag{Eq. S3a}
$$

$$
E_{HF, t+1} = \lambda_{F, t} S_{HF, t} + (1 - v_H) E_{HF, t}
$$
 (Eq. S3b)

$$
I_{HF,t+1} = v_H E_{HF,t} + (1 - r_H) I_{HF,t}
$$
 (Eq. S3c)

$$
R_{HF,t+1} = R_{HF,t} + r_H I_{HF,t}
$$
\n
$$
(Eq. S3d)
$$

With the force of infection in the farming group $\lambda_{F,t}$:

$$
\lambda_{F,t} = 1 - \exp\left(-\left(\beta_{L-H,t}^V + \beta_{L-H}^C\right)\sum_{a=1}^{10} I_{a,t}\right)
$$
\n(Eq. S3e)

and the number of S_{HF} $_{t0}$ at t_0 :

$$
S_{HF,t0} = N_H P_{HF} \tag{Eq. S3f}
$$

In the 'non-farming' group, the model is expressed as follows (Eq. S4a-S4f):

$$
S_{HNF,t+1} = \left(1 - \lambda_{NF,t}\right)S_{HNF,t} \tag{Eq. S4a}
$$

$$
E_{HNF,t+1} = \lambda_{NF,t} S_{HNF,t} + (1 - v_H) E_{HNF,t}
$$
\n(Eq. S4b)

$$
I_{HNF, t+1} = v_H E_{HNF, t} + (1 - r_H) I_{HNF, t}
$$
 (Eq. S4c)

$$
R_{HNF,t+1} = R_{HNF,t} + r_H I_{HNF,t}
$$
\n
$$
(Eq. S4d)
$$

With the force of infection in the non-farming group $\lambda_{\tiny{NF},t}$:

$$
\lambda_{NF,t} = 1 - \exp\left(-\beta_{L-H,t}^V \sum_{a=1}^{10} I_{a,t}\right)
$$
 (Eq. S4e)

and the number of $S_{NHF,t0}$ at t_0 :

$$
S_{HNF,t0} = N_H \left(1 - P_{HF}\right) \tag{Eq. S4f}
$$

βL−^H ^C was the transmission parameter corresponding to the rate at which an individual in the farming group becomes infected following direct contact with infectious livestock from all age groups (*Ia,t*), between *t* and *t+1.* This rate was assumed to remain constant over time. *βL[−] ^H ,t ^V* was the transmission parameter corresponding to the rate at which humans acquire infection from infectious livestock from all age groups (*Ia,t)* through the mediation of vectors, between time *t* and *t+1. β* $^V_{L−H,t}$ was assumed to vary over time as a function of rainfall, and was defined relative to *βL−^L ,t* (Eq. S2a and S2b), such as :

$$
\beta_{L-H,t}^V = X \beta_{L-L,t} \tag{Eq. S5}
$$

With $X \in [0,1]$, the human vector transmission scaling factor (Table S2), defining the rate of transmission from livestock to humans, relative to within livestock transmission.

The parameters β^C_{L-H} and X are also estimated by fitting the model to data (see paragraph on model fitting).

The weekly number of human incident cases in the farming $Inc_{HF,w}$ and the non-farming Inc_{HNF} *w* groups are expressed as follows:

$$
Inc_{HF,w} = \sum_{t=1}^{7} v_H E_{HF,t}
$$
\n
$$
Inc_{HNF,w} = \sum_{t=1}^{7} v_H E_{HNF,t}
$$
\n
$$
(Eq. S6a)
$$
\n
$$
(Eq. S6b)
$$

The weekly number of incident cases resulting from direct contact Inc_{w}^{C} and vector-mediated Inc^V_w transmissions were equal to:

$$
Inc_w^C = \sum_{t=1}^7 v_H E_{HF,t} \frac{\beta_{L-H}^C}{\beta_{L-H}^C + \beta_{L-H,t}^V}
$$
 (Eq. S6c)

$$
Inc_w^V = Inc_{HNF,w} + \sum_{t=1}^{7} v_H E_{HF,t} \frac{\beta_{L-H,t}^V}{\beta_{L-H}^V + \beta_{L-H,t}^V}
$$
 (Eq. S6d)

Model fitting and parameter estimation

We fitted the model simultaneously to livestock and human data by sampling from the posterior distributions of all five parameters $\theta \!=\!\! \left| A,B,\pmb{\beta}^C_{L-H},X,I_{L,t0}\right|$, using a Monte Carlo Markov Chain Metropolis-Hastings algorithm (5), and assuming uniform priors (Table S2).

Fitting the model to livestock data. The estimation of parameters was done by fitting the quarterly (q) age-stratified simulated proportion of immune livestock $p_{a,q}$, to the quarterly agestratified serological data from January to June 2019 (Table S8). The fitting was done over two trimesters (noted *q)* , January to March 2019, and April to June 2019, such as :

$$
p_{a,q} = R_{a,q} / N_a, a \in [1,10]
$$
 (Eq. S7a)

The number of positive IgG animals per quarter in the age-group $a, x_{a,q}$ among the $n_{a,q}$ tested over that same period of time, followed a binomial distribution :

$$
X_{a,q} \sim \text{Bin}\left(n_{a,q}, p_{a,q}\right) \tag{Eq. S7b}
$$

The log-likelihood of the livestock data *Loglik*^{*was*} expressed as follows :

$$
Loglik_{L}(data|\theta) = \sum_{q} \sum_{a} l_{La,q} (x_{a,q}, n_{a,q}|\theta)
$$
 (Eq. S7c)

with :

$$
Loglik_{La,q}(x_{a,q}, n_{a,q}|\theta) = x_{a,q} \log p_{a,q} + (n_{a,q} - x_{a,q}) \log (1 - p_{a,q})
$$
 (Eq. S7d)

Fitting the model to human data. We fitted (i) the simulated weekly number of reported incident cases in the 'farming' population *Cases_{HF,w*} to the observed cases reporting a contact with animals *y HF, ^w* (Table 9, Fig. 1B, Eq. S8a-S8d) and (ii) the simulated weekly number of reported incident cases in the 'non-farming' population *Cases_{HNF, w}* to the observed cases not reporting a prior contact with animals *y HNF,w* (Table 9, Fig. 1C, Eq. S9a-S9d) ; and *ρ* being the reporting fraction. The observed weekly number of reported human cases in the farming and non-farming groups, noted $y_{HF,w}$ and $y_{HNF,w}$ followed a Poisson distribution, and the corresponding loglikelihood *LogLik_{HF}* and *LogLik_{HNF}* are presented in the following equations.

For cases assumed to result from the farming group:

$$
Cases_{HF,w} = \rho \cdot Inc_{HF,w} \tag{Eq. S8a}
$$

$$
y_{HF,w} \sim Pois\left(Cases_{HF,w}\right) \tag{Eq. S8b}
$$

$$
LogLik_{HF}(data|\theta) = \sum_{w} LogLik_{HF,w}(y_{HF,w}|\theta)
$$
\n(Eq. S8c)

$$
LogLik_{HF,w}(y_{HF,w}|\theta) = \sum_{week} (y_{HF,w}) \log Cases_{HF,w} - Cases_{HF,w} - \log (y_{HF,w}!) \quad \text{(Eq. S8d)}
$$

Similarly, the log-likelihood for cases assumed to result from the non-farming group :

$$
Cases_{HNF,w} = \rho \, Inc_{HNF,w} \tag{Eq. S9a}
$$

$$
y_{HNF,w} \sim Pois(Cases_{HNF,w})
$$
 (Eq. S9b)

$$
LogLikHNF |data| \theta) = \sum_{week} LogLikHNF,w | yHNF,w | \theta
$$
 (Eq. S9c)

$$
LogLik_{HNF,w}(y_{HNF,w}|\theta) = \sum_{week} (y_{HNF,w}) log \, \text{Cases}_{HNF,w} - \text{Cases}_{HNF,w} - \log (y_{HNF,w}!) \qquad \text{(Eq. S9d)}
$$

The overall log-likelihood of the data *LogLik_{all*}, livestock and human, is given by :

$$
LogLikall(data | \theta) = LogLikL(data | \theta) + LogLikHF(data | \theta) + LogLikHNF(data | \theta)
$$
 (Eq. S10)

We ran two MCMC-MH chains of 100,000 iterations (5). We checked for convergence to the same stationary distribution. We discarded the first 10,000 iterations of the burn-in periods and thinned at a ratio of 1:10 to eliminate auto-correlation. We then combined both chains. The values of the median, 95% Credible Interval (CrI) of the posterior distributions for each estimated parameter are presented in Table S3, and for each case ('base case', '21-days lag case, and '10- 90 case').

Vaccination forecasts

Using the 'base case' estimated parameters we simulated vaccination scenarios. The expected number of efficacious doses *V ed* administered (to livestock or humans) followed a binomial distribution, with *V* being the number of vaccine doses, and *Ve* the vaccine efficacy :

$$
V_{ed} \sim Bin(V, V_e) \tag{Eq. 11a}
$$

For livestock, the number of doses administered was based on potential emergency vaccination feasible in Mayotte. For humans, since no vaccine exists yet, the number of vaccine doses administered in both farming V_{edF} and non-farming V_{edNF} groups were set as a percentage vaccination coverage of the farming V_{CHF} and non-farming V_{CHNF} populations, so that :

$$
V_{\text{edF}} = V_{\text{CHF}} N_H P_{\text{HF}} \tag{Eq. 11b}
$$

$$
V_{edNF} = V_{CHNF} N_H P_{HNF}
$$
 (Eq. 11c)

The number of efficacious vaccines administered at time *t* (to livestock or humans), *V ed ,t* , followed a multinomial distribution, with n_{days} being the length of the vaccination campaign in days:

$$
V_{ed,t} \sim Multinom(V_{ed}, n_{days})
$$
 (Eq. 11d)

For livestock, the daily number of efficacious vaccines administered per age-group a, $V_{\text{aed},t}$, followed a multinomial distribution, accounting for the proportion of livestock per age-group (*Pa*), as per the age-population structure of the underlying livestock demographic structure (1):

$$
V_{\text{aed},t} \sim \text{Multinom}\left(V_{\text{ ed},t}, P_a\right) \tag{Eq. 11e}
$$

Over the period of the vaccination campaign, and every day, vaccinated individuals or livestock moved from Susceptible livestock (S) to Susceptibles Vaccinated (SV). Susceptibles Vaccinated (SV) moved to Protected Vaccinated (PV) at a rate *γ* corresponding to the time to build-up immunity. During that time, a fraction of SV could become infected and move to *E* (Fig. S1). For livestock, indexing by yearly age-group *a*, the corresponding vaccination equations are expressed as follows in the Eq. S12a-S12d. The equations for humans are expressed similarly, without the yearly age-group index *a* :

$$
S_{a,t+1} = S_{a,t} - V_{aed,t} + [...] \tag{Eq. 12a}
$$

$$
SV_{a,t+1} = SV_{a,t} + V_{aed,t} - \lambda_{L-L,t} SV_{a,t} - \gamma SV_{a,t}
$$
 (Eq. 12b)

$$
PV_{a,t+1} = PV_{a,t} + \gamma SV_{a,t} \tag{Eq. 12c}
$$

$$
E_{a,t+1} = PV_{a,t} + \lambda_{L_t,t} SV_{a,t} + [...] \tag{Eq. 12d}
$$

Fig. S1. Model diagram showing vacination. Susceptibles (S) moved to Vaccinated Suceptibles (VS) upon vaccination with V_{ed} doses. VS moved successively to Vaccinated Protected (VP) at a γ rate, corresponding to the time to build-up immunity. During that time, VS could also become infected (E), from infectious livetock.

Fig. S2AC. Time-varying transmission parameters over the fitting period. (A) Rainfall-dependent reproductive number *Rs ,t* **(B) Transmission rate amongst livestock** *βL−^L ,t* **, (C) Vector-mediated transmission rate from humans to livestock** $\beta_{L-H,t}^V$. Median (green line) and 95%CrI (green envelopes). The vertical dotted blue lines show the time of the highest values, and the solid blue lines the time of the predicted epidemic peak. The vertical black line corresponds to the end of the fitting period (August 2019).

Table S3. Estimated parameters (median, 95% credible intervals CrI) and corresponding predicted epidemic sizes and timing of the peaks. Parameters were estimated for three cases: (1) the 'base case', defined by a proportion of the farming population set at *PHF=30%* and a 14-days rainfall lag; (2) the '21-days lag case' defined by *PHF=30%* and a 21-days rainfall lag; and (3) the '10-90 case' defined by *PHF=10%* and a 14-days rainfall lag.

Table S4. Model results for the farming (P_{HF} =30%) and non-farming (P_{HNF} =70%) group. Predicted median of total number of cases, the proportion of cases resulting from vector and direct contact transmissions, and post-epidemic seroprevalence in humans.

Table S5. Model results for the farming (P_{HF} =10%) and non-farming (P_{HNF} =90%) group. Predicted median of total number of cases, the proportion of cases resulting from vector and direct contact transmissions, and post-epidemic seroprevalence in humans.

Table S6. Number of illegally imported livestock seized by the Veterinary Services and tested against RVF IgM, between May and October 2018 (Source : Mayotte Veterinary Services)

Table S7. Number of livestock sampled and tested against RVF IgG, between July 1st 2018 and June 30th 2019, and type of sampling

Age-group (y)	Group number	Jul-Sept 2018 (Fig. 1D)	Jan-Mar 2019 (Fig. 1E)	Apr-Jun 2019 (Fig. 1 F)
<= 1year-old	1	0.00 (0.00-43.45) [0/5]	27.27 (13.15-48.15) [6/22]	75.00 (30.06-98.72) [3/4]
$1 - 2$	2	0.00 0.00-13.32) [0/25]	17.24 (7.60-34.55) [5/29]	57.14 (25.05-84.18) [4/7]
$2 - 3$	3	4.17 (0.21-20.24) [1/24]	29.03 (16.10-46.59) [9/31]	73.33 (48.05-89.10) [11/15]
$3 - 4$	4	0.00 (0.00-13.80) [0/24]	43.75 (28.17-60.67) [14/32]	62.50 (30.57-86.32) [5/8]
$4 - 5$	5	0.00 (0.00-20.39) [0-15]	40.00 (21.88-61.34) [8/20]	60.00 (31.27-83.18) [6/10]
$5-6$	6	9.52 (2.65-28.91) [2/21]	31.58 (15.36-53.99) [6/19]	100.00 (51.01-100.00) [4/4]
$6 - 7$		8.33 (0.43-35.39) [1/12]	13.33 (3.74-37.88) [2/15]	75.00 (30.06-98.72) [3/4]
$7-8$	8	6.67 (0.85-56.35) [1/6]	43.75 (23.10-66.82) [7/16]	40.00 (11.76-76.93) [2/5]
$8 - 9$	9	0.00 (0.00-27.75) [0/10]	30.77 (12.68-57.63) [4/13]	100.00 (34.24-100.00) [2/2]
> 9 years-old	10	45.16 (29.16-62.23) [14/31]	65.45 (52.25-76.64) [36/55]	87.50 (52.91-99.36) [7/8]

Table S8. Quarterly age-stratified IgG seroprevalence (95% CI) data in livestock. [number IgG positive / number tested]

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