

Identifying main drivers and testing control strategies for CCHFV spread

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Received: 25 November 2014 / Accepted: 5 June 2015 / Published online: 15 July 2015
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Abstract Crimean Congo Haemorrhagic Fever (CCHF) is an emerging zoonotic disease. The causative agent is a virus (CCHFV), mainly transmitted by ticks of the species *Hyalomma marginatum* in Eastern Europe and Turkey. In order to test potential scenarios for the control of pathogen spread, the basic reproduction number (R_0) for CCHF was calculated. This calculation was based on a population dynamics model and parameter values from the literature for pathogen transmission. The tick population dynamics model takes into account the major processes involved and gives estimates for tick survival from one stage to the other and number of feeding ticks. It also considers the influence of abiotic (meteorological variables) and biotic factors (host densities) on model outputs, which were compared with data collected in Central Anatolia (Turkey). R_0 computation was thereafter used to test control strategies and especially the effect of acaricide treatment. Simulation results indicate that such treatments could have valuable effects provided that the acaricide is applied regularly throughout the spring and summer, and over several years. Furthermore, a sensitivity analysis to abiotic and biotic factors showed that, even though temperature has a strong impact on model outputs, host (mainly hare) densities also play a role. The kind of model we have developed provides insight into the ability of different strategies to prevent and control disease spread and has proved its relevance when associated with field trials.

Electronic supplementary material The online version of this article (doi:[10.1007/s10493-015-9937-9](https://doi.org/10.1007/s10493-015-9937-9)) contains supplementary material, which is available to authorized users.

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Keywords CCHF · Basic reproduction number · Modelling · *Hyalomma marginatum* · Acaricide · Sensitivity analysis

Introduction

Crimean Congo Haemorrhagic Fever (CCHF) is a zoonotic disease that has re-emerged in Eurasia in recent years. In Turkey, an increase in human cases has been reported since 2002, with a peak in 2008–2009 (Mertens et al. 2013). More than 7000 cases were recorded during the period 2002–2012, 5 % of which were fatal. A similar re-emergence was observed in Kosova following the conflict in 1999 (Jameson et al. 2012). Tick bite is recognized as the main route of virus transmission (Mertens et al. 2013). *Hyalomma* spp. have been identified as the main vector of CCHF virus (CCHFV), in Eurasia more particularly the species *Hyalomma marginatum* (European Food Safety Authority 2010). Other routes of transmission, involving contact with an infectious patient or with blood or tissues from viraemic livestock, have also been reported (Ergonul 2006) but appear to be of much less importance.

The reasons for the re-emergence of CCHF are complex and multi-factorial. Estrada-Pena et al. (2010) identified habitat fragmentation as a major factor involved in CCHF spread in Turkey, as compared with climate-associated variables. Habitat patchiness would in this case create isolated populations of ticks and hosts, resulting in an amplification cycle of the pathogen. The Turkish outbreak in 2002 is associated with a previous decline in agricultural activities, which led to an increase in scrub vegetation and therefore suitable habitats for *Hyalomma* ticks, which resulted in great exposure of humans and domestic animals to ticks (Mertens et al. 2013). The same factors were identified to explain re-emergence of the disease in Kosova (Jameson et al. 2012).

Mathematical modelling provides an appropriate tool for the synthesis of biological processes, assessment of their influence on system dynamics, as well as the simulation of different scenarios. A model can be used to identify those factors which have a pivotal role in disease dynamics, for instance through an elasticity analysis that allows assessment of the relative contributions of different biological processes to pathogen spread (Matser et al. 2009). A modelling approach is also useful to test different strategies to control the disease. In the case of tick-borne diseases, acaricide treatments are widely used and such treatments have been tested for various tick and pathogen species (Hoch et al. 2012; Sutton et al. 2012; Porter et al. 2013; Walker et al. 2014).

When modelling disease spread, the basic reproduction number R_0 is a commonly used tool to assess the probability of a disease to spread or to become extinct (Heesterbeek 2002). R_0 computation allows the estimation of the effort to be carried out in order to eradicate or lower disease spread below acceptable levels. Hartemink et al. (2008) published a method to compute R_0 for tick-borne diseases through the calculation of a next-generation matrix. Based on this method, elasticity analyses were performed on R_0 values for several tick-borne diseases, amongst whom CCHF (Matser et al. 2009). In these cases, R_0 was calculated thanks to empirical values for tick feeding numbers and survival rates. Estrada-Peña et al. (2013) elaborated risk maps for CCHF based on spatial estimations of R_0 to highlight factors driving the possible expansion of the disease. They used a previously published population dynamics model of *H. marginatum* (Estrada-Pena et al. 2011) to assess the influence of meteorological variables on R_0 values. However, their model did

not explicitly consider the tick hosts and their influence on year-to-year survival and pathogen acquisition rates.

In order to disentangle the respective influences of biotic (host densities) and abiotic (temperature and humidity) factors on CCHFV spread, there is thus a need to develop a model that takes into account both these factors. Our objective here was to estimate the basic reproduction number for CCHF, based on a population dynamics model that accounts for meteorological variables and host densities. R_0 values were used thereafter to identify the key factors influencing CCHF spread and to test different strategies for controlling disease spread.

Methods

Biological concepts

The main stages and processes involved in the *H. marginatum* population and CCHF transmission dynamics are summarized in a flow diagram (Fig. 1). The stages considered in the *H. marginatum* population dynamics were eggs, larvae, nymphs and adults. Larvae and adults could be either questing, feeding or in development, whereas no questing phase was considered for nymphs. As a specific feature for this tick, larvae moult on host and nymphs directly feed on the same host. Hatching, host finding, feeding and development durations, egg laying and mortality at each phase represent the main involved processes. *H. marginatum* needs two hosts to complete its cycle: we assumed that hares represented the main host for immature stages, even though hedgehogs and ground-feeding birds might play a role, and cattle were considered preferential feeding hosts for adult ticks.

Infection spreads through the following processes: transmission (from tick to host) and acquisition (from host to tick) of the pathogen, transstadial persistence, transovarial transmission and clearance of the pathogen in both hosts. Only systemic transmission during feeding was considered in our model: transmission from infectious larvae and

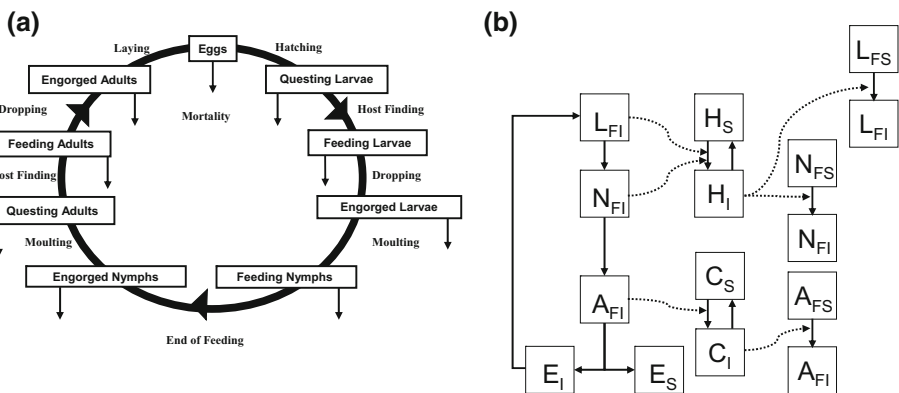


Fig. 1 Flow diagram of the model: **a** tick population dynamics model, **b** infection model. For the latter, only processes that play a role in pathogen spread are shown. *H* and *C* represent hare and cattle variables, respectively. *E*, *L*, *N* and *A* are used for eggs, larvae, nymphs and adult ticks, which could transmit or acquire the pathogen during the feeding phase (subscript *F*). Hosts and ticks are either susceptible (subscript *S*) or infectious (*I*)

nymphs to hares, and from adults to cattle (and acquisition in the reverse sense). Rare experiments on transmission through co-feeding larvae and nymphs have demonstrated the low transmission potential of this process (Gordon et al. 1993). Matser et al. (2009), after performing an elasticity analysis, underlined the pre-eminence of systemic and transovarial transmission processes to maintain infection. We therefore assumed that transmission through co-feeding could be neglected.

R₀ calculation

Calculation of the basic reproduction number for vector-borne diseases is tricky, especially when the different stages at which the vector can acquire the pathogen and the different competent hosts are taken into account. Hartemink et al. (2008) overcame this complexity by building a next-generation matrix K , whose largest eigenvalue gives the basic reproduction number. Each element k_{ij} of the matrix represents the expected number of infectious individuals of one type i produced by an infectious individual of another type j , which corresponds to the type at the moment of infection, called “type-at-birth”. Six “types-at-birth” were considered in our case: eggs (E), feeding larvae (L), nymphs (N) and adults (A) for the tick (indices 1–4) and two host compartments (H for hares and C for cattle) with respective indices 5 and 6. The next-generation matrix could therefore be written as follows:

$$K = \begin{pmatrix} t_{ov} & t_{ov} & t_{ov} & t_{ov} & 0 & 0 \\ 0 & 0 & 0 & 0 & H \rightarrow L & 0 \\ 0 & 0 & 0 & 0 & H \rightarrow N & 0 \\ 0 & 0 & 0 & 0 & 0 & C \rightarrow A \\ E \rightarrow H & L \rightarrow H & 0 & 0 & 0 & 0 \\ E \rightarrow C & L \rightarrow C & N \rightarrow C & 0 & 0 & 0 \end{pmatrix} \quad (1)$$

$$= \begin{pmatrix} k_{11} & k_{12} & k_{13} & k_{14} & 0 & 0 \\ 0 & 0 & 0 & 0 & k_{25} & 0 \\ 0 & 0 & 0 & 0 & k_{35} & 0 \\ 0 & 0 & 0 & 0 & 0 & k_{46} \\ k_{51} & k_{52} & 0 & 0 & 0 & 0 \\ k_{61} & k_{62} & k_{63} & 0 & 0 & 0 \end{pmatrix}$$

where t_{ov} represents transovarial transmission. The number of infected eggs in the next generation caused by one infected egg (k_{11}) could be estimated as follows:

$$k_{11} = s_L \cdot s_N \cdot s_A \cdot s_P \cdot Fec \cdot R_E, \quad (2)$$

where s is the survival probability, from egg to feeding larva stage (s_L), from feeding larva to feeding nymph stage (s_N), from feeding nymph to feeding adult stage (s_A), and of the female in preoviposition (s_P), respectively. Fec represents the number of eggs laid per female and R_E the probability of transovarial transmission.

The transmission term, for instance from an infected egg to a hare, could be expressed by the following equation:

$$k_{51} = s_L \cdot R_L + s_L \cdot s_N \cdot R_N, \quad (3)$$

where R_L and R_N are the transmission probability from larvae and nymphs, respectively, to hares. And similarly, from an infected egg to a bovine:

$$k_{61} = s_L \cdot s_N \cdot s_A \cdot R_A, \quad (4)$$

with R_A the transmission probability from adults to cattle.

As for acquisition, the average number of adult ticks that become infected after feeding on one infectious bovine is calculated as follows:

$$k_{46} = \frac{d_{InfC} \cdot \left(\frac{\bar{A}_F}{HD_C} \right) \cdot P_A}{d_{FeedA}}, \quad (5)$$

where $\frac{\bar{A}_F}{HD_C}$ and P_A represent the average number of feeding adult per host (HD_C = Cattle density) and the efficiency of the acquisition process, respectively. The parameters d_{InfC} and d_{FeedA} refer to the respective durations of the infectious period in cattle and of the feeding period for adult ticks.

The other terms of the next-generation matrix, regarding either transovarial transmission, transmission by feeding ticks or acquisition, are calculated in a similar way to the above equations, with appropriate parameter values.

We developed a population dynamics model to estimate the survival probabilities from one stage to the next and the average number of feeding ticks ($\bar{A}_F$ for adults), respectively. These quantities were estimated numerically from this model. Parameters describing CCHFV transmission were taken from the literature.

Hyalomma marginatum population dynamics model

The model is based on the population dynamics described in Fig. 1. On account of modelling assumptions, with daily cohorts in development phases, we chose to develop a discrete-time model with a 1-day time-step. It is deterministic, as large numbers of individuals in each stage do not require stochasticity. The following system describes the equations used for the larva compartment:

$$\begin{cases} L_Q(t+1) - L_Q(t) = E_{k>1}(t) - L_Q(t) \cdot (\delta_L + \mu_{LQ}) \\ L_F(t+1) - L_F(t) = L_Q(t) \cdot \delta_L - L_F(t) \cdot (\gamma_L + \mu_{LF}) \\ L_D(t+1) - L_D(t) = L_F(t) \cdot \gamma_L - L_D(t) \cdot \mu_{LD} - L_{Dk>1}(t) \end{cases} \quad (6)$$

Q , F and D apply to the questing, feeding and development phases, respectively. Similar equations are used for nymphs (without the questing phase) and adults. The parameters μ and γ represent the mortality and engorgement rates, respectively, and δ is the rate at which questing individuals find a host. $L_{Dk>1}(t)$ [or $E_{Dk>1}(t)$] is the number of larvae that have completed their development at time t (or eggs that have hatched).

Mortality rates during questing and development were derived from equations published by Estrada-Pena et al. (2011), where the rates were dependent on temperature (θ_t) and vapour pressure deficit (VPD_t) at time t of the year. These authors also fitted equations for the development duration of eggs, nymphs and adults, and the inverse values are used as daily development rates in our model. They considered that the duration of the development phase from larvae to nymphs was constant. Similar to Ogden et al. (2005) for *Ixodes scapularis* and Hoch et al. (2010) for *I. ricinus*, we considered that the development of a daily cohort of ticks was completed when the sum of the daily development rates (k) for this cohort was equal to 1. Equations for these mortality and development rates using θ_t and VPD_t are detailed in Appendix S1 (online supplementary material).

On account of the work by Ogden et al. (2005), we adopted a density-dependent mortality rate for feeding individuals. We therefore assumed that the mortality rate during

Table 1 Name, meaning, value, unit and associated reference for the parameters used in the model

Name	Meaning	Value	Unit	References
Fec	Number of eggs per laying female	6500	Eggs	Estrada-Pena et al. (2011)
d_{FeedL}	Duration of the feeding period for larvae	5	Days	Estrada-Pena et al. (2011)
d_{FeedN}	Duration of the feeding period for nymphs	8	Days	Estrada-Pena et al. (2011)
d_{FeedA}	Duration of the feeding period for adults	14	Days	Estrada-Pena et al. (2011)
μ_F	Basal mortality rate during feeding	0.28	Day ⁻¹	Estimated
α	Influence of density dependence on mortality	0.1	Day ⁻¹	Estimated
HD_H	Hare density	3.4	Number ha ⁻¹	Flux and Angermann (1990)
HD_C	Cattle density	1	Number ha ⁻¹	Sutton et al. (2012)
η_L	Basal finding rate for larvae	0.0041	Day ⁻¹ individual ⁻¹ (°C) ⁻¹	Estrada-Pena et al. (2011)
η_A	Basal finding rate for adults	0.06	Day ⁻¹ individual ⁻¹ (°C) ⁻¹	Estrada-Pena et al. (2011)
λ_L	Exponent relating temperature and finding rate for larvae	0.51	–	Estrada-Pena et al. (2011)
λ_A	Exponent relating temperature and finding rate for adults	0.49	–	Estrada-Pena et al. (2011)
d_{InfH}	Infection duration in hares	5	Days	Matser et al. (2009)
d_{InfC}	Infection duration in cattle	7	Days	Matser et al. (2009)
R_E	Efficiency of transovarial transmission	0.17	–	Matser et al. (2009)
R_L	Efficiency of the transmission from larva to host	0.2	–	Matser et al. (2009)
R_N	Efficiency of the transmission from nymph to host	0.2	–	Matser et al. (2009)
R_A	Efficiency of the transmission from adult to host	0.2	–	Matser et al. 2009
P_L	Efficiency of the acquisition by larva	0.3	–	Matser et al. (2009)
P_N	Efficiency of the acquisition by nymph	0.3	–	Matser et al. (2009)
P_A	Efficiency of the acquisition by adult	0.3	–	Matser et al. (2009)
E_0	Initial acaricide efficiency	0.9	–	Hoch et al. (2012)
P	Parameter determining inflexion of efficiency curve	0.5	–	Hoch et al. (2012)
hl_E	Half-life of acaricide	20	Days	Hoch et al. (2012)

feeding increased with the number of ticks per host, on account of grooming and the immune response. The equation is as follows, for all tick stages ($T = L, N$ or A):

$$\mu_{TF} = \mu_{F0} + \alpha \cdot \ln \left(1 + \frac{T_F}{HD_i} \right), \quad (7)$$

where μ_{F0} and α are, respectively, the basal rate and a factor that defines the influence of host density. HD is used for host density and subscript i refers to the type of host (H for hares, C for cattle).

Estrada-Pena et al. (2011) considered that the host-finding rate for larvae and adults was only dependent on temperature. We included a dependency on host density as this is recognized to have an influence (Mount et al. 1993; Ogden et al. 2005). We assumed that the host-finding rate increased linearly with host density, as no information exists about the form of the relationship. Host-finding rate is thus calculated with the following equation:

$$\delta_T = \eta_T \cdot HD_i \cdot \theta_t^{\lambda_T}, \quad (8)$$

where η and λ are parameters applied to questing larvae or adults ($T = L$ or A). With the chosen parameter values, δ_T always lies between 0 and 1 at current temperatures.

Parameter and data

The parameters used to calculate R_0 are summarized in Table 1. Parameter values were taken from the literature when available and were mostly derived from the Estrada-Pena et al. (2011) and Matser et al. (2009) models. A calibration step has been carried for some parameters related to *H. marginatum* mortality and development, using field data.

Meteorological conditions, in terms of temperature and water vapour pressure, were chosen for a location situated in a CCHF-endemic area in central Anatolia (Yozgat district, coordinates: 39°30'N, 35°00'E). Mean monthly data were available from New_LocClim (http://www.fao.org/nr/climpag/pub/en3_051002_en.asp) for temperature and water vapour pressure. Annual mean (θ_{mean}) and amplitude (θ_{amp}) were fitted on the monthly temperature data at this site so that the daily temperature (θ_t , in °C) can be expressed as follows:

$$\theta_t = \theta_{mean} + \theta_{amp} \cdot \sin \left(\frac{2\pi t}{365} - \varphi t \right), \quad (9)$$

where φ is a parameter that determines the phase (see Appendix S2 (online supplementary material) for details on parameter estimation).

Vapor pressure deficit (in hPa) is given by the equation:

$$VPD_t = e_{st} - e_{at}, \quad (10)$$

where e_{at} is the amount of moisture in the air, given by the data, and e_{st} the maximum water holding capacity, which increases with temperature through the following relationship:

$$e_{st} = 0.6108 \exp \left(\frac{17.27\theta_t}{237.3 + \theta_t} \right). \quad (11)$$

Data on *H. marginatum* consisted of mean numbers of adult ticks per bovine and were used to calibrate the population dynamics model. Ticks were collected on 459 cattle, 91.3 % of which were infested, in Yozgat district during a longitudinal study in spring and summer 2013 (Vatansever, unpublished data).

Simulations, test of control strategies and sensitivity analysis

The simulation of the tick population dynamics was initiated by considering 100 eggs, questing larvae and adults. The results of the simulation are not dependent on initial conditions as the model was first run for 30 years so as to reach quasi equilibrium output values. The basic reproduction number computed in the nominal simulation, the acaricide treatments test and the simulations for the sensitivity analyses was obtained with initial conditions equal to the values for the variables obtained at the end of the 30-year simulations.

R_0 computation was carried out for each simulation and requires estimation of survival probabilities and average number of feeding ticks. Survival probabilities correspond to the ratio between total number of ticks generated during 1 year for one stage to the corresponding number for the previous stage (e.g., engorged nymphs/engorged larvae). The number of feeding ticks is averaged over 1 year to obtain $\bar{L}_F$, $\bar{N}_F$ and $\bar{A}_F$.

The model enabled us to simulate the influence of acaricide treatment, applied to cattle, on pathogen spread. Like Hoch et al. (2012) who simulated the effect of acaricide treatment on bovine babesiosis, we considered that acaricide efficiency, which corresponded to an additional mortality rate for feeding adult ticks, was maximal at the beginning of treatment and then declined following the formula:

$$E_t = E_0 \cdot \left(1 - \frac{1}{1 + e^{-\gamma \cdot (t - hl_E)}} \right), \quad (12)$$

where E_0 represents the initial efficiency level, hl_E is the time at which the initial efficiency is halved and γ is a parameter determining the inflexion of the curve.

Acaricide was first applied at the beginning of April. Several strategies were tested with different starting dates, treatment numbers and intervals between treatments. The influence of these strategies was assessed by calculating the variation in R_0 after 1 year and 5 years of simulated treatments, respectively.

A sensitivity analysis was then performed to classify the respective effects of biotic (host densities) and abiotic (meteorological variables) factors on R_0 values. The values for these factors were sampled by applying the FAST method (Saltelli et al. 2000). Each factor (hare and cattle densities, mean and amplitude of the temperature and a factor affecting daily values for VPD , with an initial value of 1) was thus sampled within a range of $\pm 15\%$ of its nominal value. A 5-year period was chosen for the simulations as some factors, especially host densities, may influence model results over several years. Simulations with the sampled parameter values were used to compute Sobol sensitivity indices for the basic reproduction number.

Simulations were carried out using SciLab software (<http://www.scilab.org>), whereas the sensitivity analysis was performed using the sensitivity package in R (<http://www.r-project.org/>).

Results

Tick population dynamics

The dynamics of the number of feeding *H. marginatum* adults per bovine are plotted in Fig. 2. The simulated dynamics roughly mimic the observed densities and phenology of

adult ticks. An estimated value of 1.18 for the basic reproduction number was obtained for the corresponding infection parameters and simulated population dynamics.

Test of acaricide treatments

The various tested strategies are listed and described in Table 2, together with their relative effect on R_0 . The conclusions differ depending on whether the short-term (after 1 year) or mid-term (5 years) effect is considered. For short-term effects, the date at which the first treatment is applied appears to be a major factor acting on the infection dynamics, the starting date being 100 (10th March) for the most effective treatment. More particularly, late treatments do not cause a large reduction in R_0 . After 5 years of simulation, the number of treatments is of major importance and the difference among strategies with 2, 3 and 4 treatments per year, respectively, increases with time. A short interval between treatments also seems to be important to achieve an effect after 1 year of treatment but the influence appears to be inversed over a longer term (strategy 2 vs. 3). It should also be noted that the R_0 values are greater than 1 after 1 year of simulation for all strategies except 2 and 4, and always below this threshold after 5 years.

Sensitivity analysis

The sensitivity indices for the basic reproduction number highlight the major influence of temperature and host densities, especially hare density, on the model results (Fig. 3). The overall effect of temperature amplitude accounts for more than 50 % of the variability in the model results, when the focus is on R_0 as model output. The contribution of total host density attains 28 % of the total variability, with values of 16 and 12 % for hare and cattle densities, respectively, whereas mean temperature contributes 15 % of the variability. Vapour pressure deficit appear to have less effect on the model outputs. It seems that the main effects of the factors are of greatest importance and that the interactions only contribute very weakly.

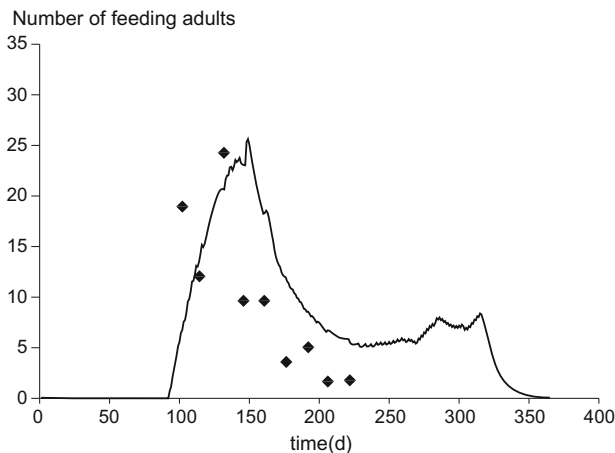
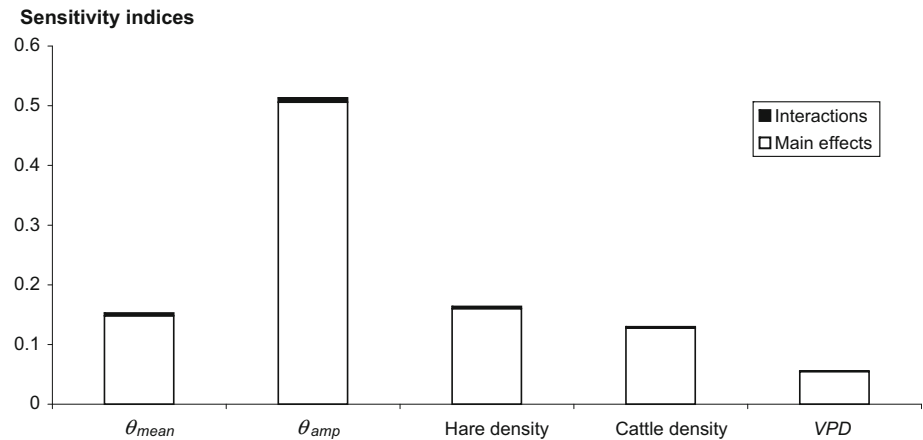


Fig. 2 Simulated dynamics for the feeding adult ticks. Comparison with data collected in Yozgat district (Central Anatolia). Data are in number of individuals per bovine

Table 2 Influence of different strategies for acaricide treatment on the variation in basic reproduction number (R_0), for two treatment durations

No.	Description of the strategy			Reduction in R_0 (in %)	
	Starting date (day number)	Number of treatments	Treatment interval (days)	After 1 year	After 5 years
1	100	2	30	−11.2	−17.6
2	100	3	30	−15.9	−26.7
3	100	3	40	−13.1	−28.2
4	100	4	30	−16.6	−33.3
5	120	3	30	−14.0	−26.8
6	150	3	30	−7.6	−20.8

**Fig. 3** Sobol sensitivity indices (no unit) for the various factors investigated, which measure their effect on R_0 . The effect of abiotic (mean and amplitude of the temperature, θ_{mean} and θ_{amp} , vapour pressure deficit, VPD) and biotic (hare and cattle densities) factors were investigated through a global analysis

Discussion

To estimate the basic reproduction number, we have developed a mechanistic model that allows the simulation of *H. marginatum* population dynamics over several years and takes into account both biotic and abiotic factors. Sutton et al. (2012) had already presented a model that aimed to simulate *Hyalomma* ticks dynamics and *Theileria annulata* transmission. However, in their model, transitions from one tick stage to another were based on fixed transition rates which did not take into account meteorological variables and their fluctuations. By considering biological processes in tick population dynamics it is possible to identify the major factors (biotic or abiotic) influencing R_0 values.

The basic reproduction number was thus calculated thanks to simulated survival probabilities and tick densities. The resulting simulated R_0 differs from the value estimated by Matser et al. (2009) with a static model (1.18 vs. 2.18) that also did not account for

meteorological influence. The variations in this estimated value may be explained by differences between the types of model used to calculate R_0 . We chose not to include non-systemic transmission in our model as the sensitivity analyses reported by Matser et al. (2009) and Estrada-Pena et al. (2013) did not indicate any evidence of a significant effect of this process. The basic reproduction number for vector-borne diseases must take both vector and host influence into account in the transmission dynamics. Charron et al. (2011), studying Bluetongue control in cattle, added some complexity to the calculation by estimating a seasonal R_0 from simulations. Such an approach could not be used in our case, due to the complexity of the tick population dynamics model. The calculation of R_0 in the test of control strategies and the sensitivity analysis would require too much simulation time if seasonal variation were taken into consideration.

More importantly than its nominal value, R_0 computation constitutes a valuable tool for testing strategies to control vector-borne disease spread. As for tick-borne diseases, acaricide treatments are the most widespread strategies and mainly target tick population control. Modelling may be helpful to determine the most effective acaricide treatment. We chose to focus on treatments that impact adults feeding on cattle as being the easiest to carry out. Therefore our study cannot be compared with the simulations made by Sutton et al. (2012) who also tested methods that targeted questing individuals by acting on the environment but whose application seems less easy. Dobson and Randolph (2011) used a matrix model for *I. ricinus* population dynamics (Dobson et al. 2011) to simulate the effect of treating variable proportions of the wild host population. Porter et al. (2013) predicted that the efficacy of acaricide treatment for controlling louping ill virus in red grouse population would depend on deer density. At low deer density, no treatment will be required whereas the number of hares needing to be treated will increase with deer density, above a given threshold. The model developed by Walker et al. (2014) for *Theileria parva* infection considered three hosts: cattle, buffalo and alternate hosts. They concluded that control strategies that only target cattle are not able to limit disease transmission in buffalo. In our model, hares and cattle are the respective hosts for immature and adult ticks, which is relevant as we focused on the Turkish agricultural landscape. In such a system, pour-on applications of acaricide appear to be effective in preventing disease transmission to cattle, provided that the treatment is repeated over several years. Efficacy is increased, but not linearly, by the number of applications.

Estrada-Pena et al. (2011) had already carried out a sensitivity analysis on the biological processes involved in *H. marginatum* population dynamics, using a One-At-a-Time analysis. Sensitivity indices were also estimated for different parameters of the CCHFV transmission model, for a large range of R_0 values (Estrada-Pena et al. 2013). We chose to focus on the forcing variables and their interactions by performing a global sensitivity analysis. Interactions between variables were not shown to play a major role in the model. The model is sensitive to air temperature, mainly to its amplitude, which makes sense, considering the effect of this variable on development and mortality rates. On the contrary, vapour pressure deficit does not seem to exert a strong influence on disease spread. Fluctuations in host densities, especially hare density, influence CCHFV spread, lowering values for densities inducing a reduction in disease spread. This is in agreement with the review by Estrada-Pena et al. (2012) in which it was suggested that CCHF epidemics would likely be related to a combination of factors, such as habitat abandonment, landscape fragmentation and an increase in wildlife host densities. A strategy to prevent disease spread could be to reduce the overlap between hare and cattle habitats in the fields.

This modelling study provides insights into factors influencing CCHF spread. Acaricide treatments, together with wildlife and cattle management, could therefore be used to lower

tick population size and consequently the CCHFV prevalence in hosts and the number of infected questing ticks, i.e., the acarological risk. Modelling could also highlight the periods and areas where the risk of being infected by CCHFV is maximal. However, to do this, our knowledge of tick ecology and pathogen transmission needs to be extended. Model accuracy and the conclusions drawn will benefit from the integration of new knowledge into existing models.

Acknowledgments This study was funded by EU grant FP7-261504 EDENext and is catalogued by the EDENext Steering Committee as EDENext340 (<http://www.edenext.eu>). The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views of the European Commission. A part of the work of ZV was also supported by the grant 108G191 of The Scientific and Technological Research Council of Turkey (TUBITAK).

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