ORIGINAL ARTICLE

Factors driving the circulation and possible expansion of Crimean–Congo haemorrhagic fever virus in the western Palearctic

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Abstract

Aims: To produce a spatial risk map regarding spread of Crimean-Congo haemorrhagic fever virus (CCHFV) in the western Palearctic by linking a process-driven model of the main tick vector, *Hyalomma marginatum*, to a Next Generation Matrix.

Methods and Results: Process-driven model was composed of deterministic equations that simulate developmental and mortality rates of different tick stages by using temperature and atmospheric water vapour data. The model used climate data at 10-day intervals at a spatial resolution of 10 min over western Palearctic. The model estimated the basic reproduction number, R0, for CCHFV transmission by *H. marginatum* ticks and evaluated how changes in temperature and biological parameters may alter the geographical range of CCHFV. In particular, variation in the rate of transovarial transmission of CCHFV in the tick produced the greatest change in CCHFV circulation in the tick population. Parameters affecting the rates of tick bite, non-systemic transmission and efficiency of tick-to-tick transmission had little effect on R0. Temperature changes that affect tick development, survival and activity rates increased the suitable area for CCHFV transmission at higher latitudes in the western Palearctic.

Conclusions: Non-systemic transmission had little impact on virus transmission under all scenarios. In the area studied, increase of temperature has no impact on the routes of transmission of CCHFV. However, climate conditions favouring tick survival, which increase infected adult tick populations, together with large numbers of hosts for adults were predicted as the most likely scenario for the spread of the virus in the studied area.

Significance and Impact of the Study: The proposed framework is able to capture the dynamics and the relative contribution of the different routes (hosts, ticks) in the transmission and spread of an important pathogen affecting human health. The high contribution of the transovarial transmission route makes the process highly dependent upon suitable hosts for adult ticks, like large domestic and wild ungulates. Climate seems to have a very reduced effect on such spread.

Introduction

Crimean–Congo haemorrhagic fever (CCHF) is a serious human disease mainly transmitted by ticks of the genus Hyalomma. Interest in the disease increased after the epidemic in Turkey and new viral records reported in areas near Turkey such as the Balkans and Russia (Ergonul and Whitehouse 2007). Studies have focused

on outlining the probable routes for virus introduction into Western Europe from the original foci of the disease in Eastern Europe and Turkey (EFSA 2010; Gale *et al.* 2010; Estrada-Peña *et al.* 2012a). The finding of CCHF virus (CCHFV) in Western Europe (Estrada-Peña *et al.* 2012b) demonstrated that the virus is not restricted to Eastern Europe. A viral strain circulating in south-western Mediterranean is a reason of concern about the spread of the virus into northern latitudes (Gale *et al.* 2011).

The tick vector has three active stages. The immature (larvae and nymphs) commonly feed on the same hosts, which are many species of small mammals and birds. Large ungulates serve as hosts for the adults. Adult female ticks contribute to the infection by transovarial transmission (vertical transmission) of the virus to the eggs (Shepherd *et al.* 1989). Feeding on infected reservoir hosts or through the nonsystemic transmission of the virus might also infect ticks. Nonsystemic transmission may occur when uninfected ticks feed on the same vertebrate host near to an infected tick, which passes the virus to the uninfected tick with the saliva without host systemic infection (Gordon *et al.* 1993). Studies on other tick-transmitted viruses such as tick-borne encephalitis virus (TBEV) demonstrated that subtle variations in field seasonal patterns of the tick vector profoundly affect the dynamics of active foci (Randolph *et al.* 2000). While a large social component has been identified behind the upsurge of tick-borne encephalitis (Šumilo *et al.* 2008), concerns exist about the spread of the virus of TBEV into areas that recently became suitable for the tick vector because of climate trends.

The spread of pathogens is typically characterized by the basic reproduction number, $R0$. This quantity is fundamental to the theory and management of infectious diseases. $R0$ is defined as the expected number of secondary cases produced by a single infected animal in a wholly susceptible population when a homogeneous and well-mixed host population exists. In the model here, $R0$ represents the number of infected Hyalomma ticks arising from introduction of a single infected tick into a population of susceptible ticks. If $R0$ is ≥ 1, the virus can persist and circulate in the tick population, otherwise it does not establish. To work with pathogens that infect multiple hosts, the next-generation matrix (NGM) was introduced (Diekmann *et al.* 1990). The number of epidemiologically distinct infected and infectious host types determines the dimension of NGM, whose entries are host-type specific $R0$ (Diekmann *et al.* 1990). A generalist NGM was developed to illustrate the basic features of transmission rates for some tick-borne pathogens (Matser *et al.* 2009).

Tick species distribution modelling alone is not valid to infer circulation of ticks-transmitted pathogens when the tick-borne pathogens depend on subtle changes in development, mortality and activity rates of the tick vectors. A dynamic study is necessary for adequate awareness of the endemic potential of CCHFV in Europe. It should explicitly consider tick seasonality, development and mortality rates at discrete time intervals and link these tick processes with the parameters governing the circulation of the virus. This approach could evaluate the effects of climate on tick seasonal processes and thus its effects on virus transmission.

In this study, we developed a dynamic model for the transmission of CCHFV in western Palearctic. The original NGM approach was improved by incorporating a process-driven model for the tick vector, *Hyalomma marginatum* that allowed estimating tick performance at short time intervals. We specifically explored how changes in the parameters of the model and variations in temperature in the western Palearctic modify the endemic potential of CCHFV in the region through their impact on virus transmission routes and/or tick developmental and survival rates.

Materials and methods

Modelling approach

We used previously developed methods for the analysis of tick-borne pathogens, based on the NGM (Hartemink *et al.* 2008; Matser *et al.* 2009; Supporting Information). Instead of using an idealized tick phenology (Davis and Bent 2011), we used a process-driven model of the tick life cycle previously developed and validated (Estrada-Peña *et al.* 2011). Therefore, basic processes governing the epidemiology of CCHFV arise from tick life cycle processes. The model was applied over the known distribution area of the main tick vector in the western Palearctic, thus accounting for the variability in virus circulation in both time and space. The impact produced on $R0$ by changes in climate factors and biological parameters of the model were incorporated to produce a dynamic picture of the epidemiological features of CCHFV. This model was not intended for high-resolution analysis, because of the existence of uncertainties at low spatial scales. Instead, it was developed to understand the patterns of virus transmission over large areas.

The *Hyalomma marginatum* life cycle model

The process-driven model for the main tick vector of CCHFV was composed of discrete, deterministic equations that convert temperature and atmospheric water vapour data into mortality and development rates of different tick stages. The model used climate data at 10-day

intervals, at a spatial resolution of 10 min over the western Palearctic, covering from 18°W, 68°N (top left corner) to 49°E, 27°N (bottom right corner). Climate values were obtained from the New LocClim software (Grieser *et al.* 2006), which includes daily estimates of temperature and water vapour obtained between 1961 and 1990. Daily climate values provided by New LocClim were converted into 10-day intervals by averaging the original data. Model development, parameterization and empirical validation were previously published (Estrada-Peña *et al.* 2011, see Supporting Information).

NGM for the simulation of *R*0 for CCHFV

Our contribution to the dynamics of *R*0 in a tick-CCHFV system is a framework to evaluate the tick phenology with the life's cycle model of the tick as driven by climate features and its impact on viral circulation routes (transovarial, systemic, nonsystemic). We otherwise adhered to published contributions (Hartemink *et al.* 2008) to build the NGM. Our approach calculated the basic 'types' of infections for tick-borne infections with a 5×5 matrix structure. The systemic transmission from ticks to hosts, the nonsystemic (cofeeding) transmission among ticks feeding simultaneously on a host (Labuda *et al.* 1993) and transovarial transmission were used in the model. Briefly, the NGM contained the numbers of individuals that are infected by one infected individual of each type-at-birth during the time it is infectious. Types-at-birth refer to ticks or hosts that become infected ('birth' of an infected, *sensu* Hartemink *et al.* 2008). Types-at-birth were labelled as (i) ticks infected as an egg, (ii) ticks infected by nonsystemic transmission, (iii) hosts infected by ticks feeding on them and (iv) ticks infected by competent hosts. The model was parameterized with transmission efficiency values taken from the literature for (i) female ticks to eggs (*R*), (ii) ticks to hosts (*P*), (iii) hosts to ticks (*Q*), and (iv) ticks to ticks. Phenology values for one complete generation of the tick then modulated the NGM values for the basic 'types' of infection. *R*0 was computed with the package 'popbio' working on the R development framework (R Development Core Team 2011).

### Sensitivity of *R*0 to changes in model parameters and temperature variations

Other than the phenology of the tick and its abundance, the transmission of the virus is further regulated by a series of biological parameters summarized by Matser *et al.* (2009), which have been considered and evaluated in laboratory studies. These parameters are *H* (fraction of tick blood meals on infective hosts), *i* (duration of host infection), *R* (efficiency of transovarial transmission), θ (efficiency of tick-to-tick transestadial transmission) and *P + Q* (transmission from hosts to ticks and *vice versa*). These parameters drive the biological aspects of the vector and the pathogen. Values of pathogen transmission rates were obtained from laboratory studies. Fixed values were used for the biotic parameters of the model, and the transmission rates were further varied over plausible ranges based on literature estimates (Tables S1 and S2). We specifically tested the effects of temperature on tick vector developmental and survival rates and thus indirectly on *R*0. This is an oversimplified approach if the effects of climate on the expected distribution of the tick are to be evaluated. However, we wanted to assess the claims on the effects of temperature alone on the tick life cycle and thus on the epidemiological potential of CCHF. Further on this, it is ignored how water vapour contents, relevant for computing of tick's processes, would change as a consequence of temperature scenarios. The use of both temperature and water vapour would generate increasing levels of complexity and uncertainty. We therefore focused only on the effects of temperature, and we used the upper and lower temperature limits (5 and 95% percentiles, respectively) recorded over the target geographical region (Grieser *et al.* 2006). After each run, the sensitivity and elasticity were computed to assess the contribution of each transmission route of the virus under each set of conditions (Matser *et al.* 2009).

Results

Potential CCHFV circulation areas in western Palearctic

A process-driven model for the life cycle of the tick vector, *H. marginatum*, showed the range of potential areas for CCHFV circulation in western Palearctic (Fig. 1a). The highest *R*0 values were observed over large areas of the Mediterranean basin, with areas of lower but ≥ 1 *R*0 values in the Balkans, northern Italy, south-western France and even parts of the United Kingdom. Changes in temperatures had a clear influence on the variations of *R*0. Low temperatures decreased *R*0 values by 96% when compared to data obtained with average temperatures (Fig. 1b). Using scenarios of high temperatures increased *R*0 by 116% (Fig. 1c). The size of the territory where $R0 \geq 1$ decreased by 87% or increased by 114% with series of low and high temperatures, respectively. As expected, the temperature had an effect on the suitable habitat for the tick vector. The range of $R0 \geq 1$ values is higher at northern latitudes when the series of higher temperatures were used. Changes in *R*0 by temperature increase (decrease) resulted in an increase (decrease) in tick abundance because of lower (higher) mortality rates
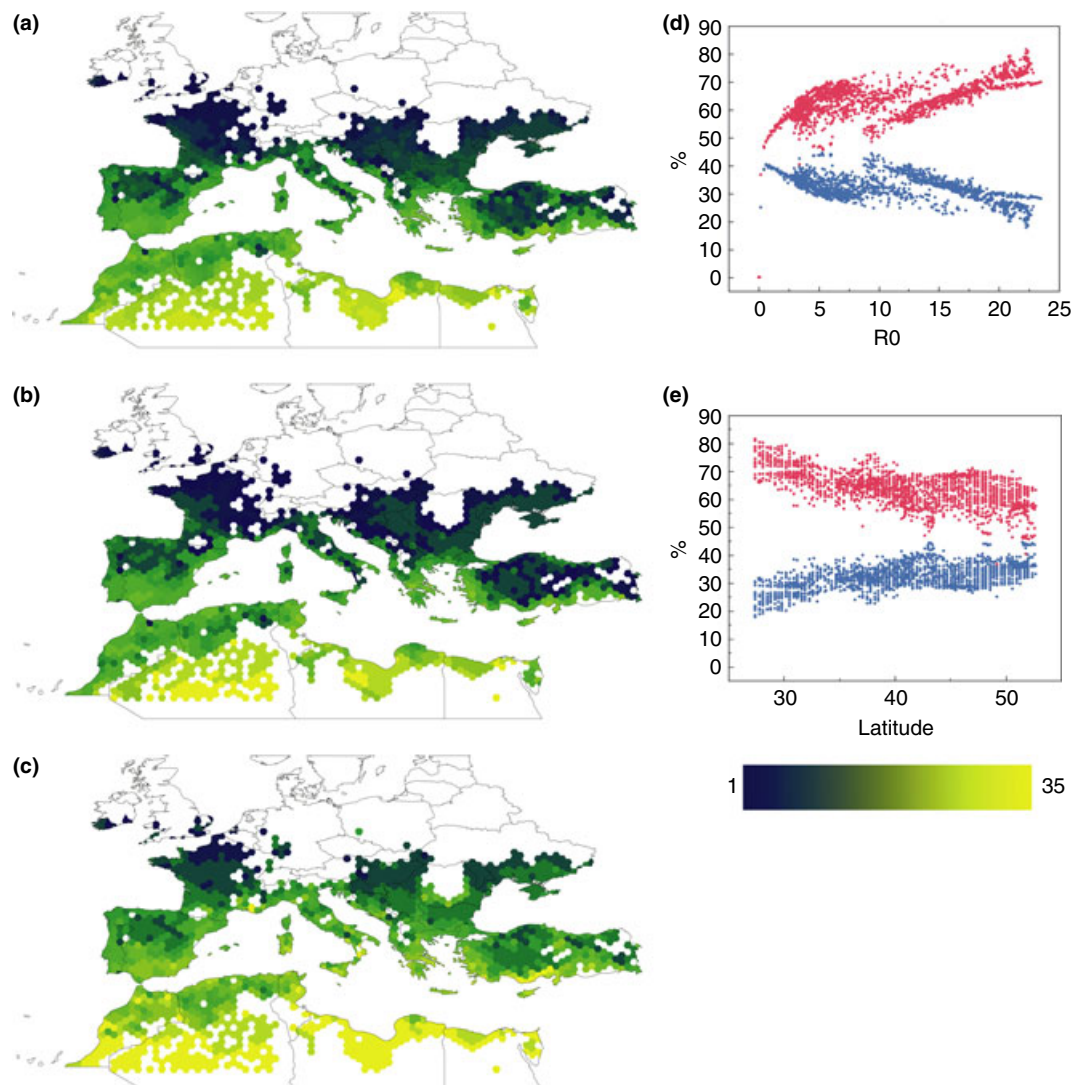
Figure 1 Basic Reproduction Rate ($R0$) for Crimean–Congo haemorrhagic fever virus (CCHFV) in western Palearctic. (a) $R0$ geographical range. (b, c) $R0$ changes in simulations with low (b) and high temperatures (c). (d, e) Contribution of the nonsystemic and transovarial transmission routes according to $R0$ (d) and the latitudinal gradient (e). (●) Non-systemic transmission; (●) transovarial transmission. Areas in white are those where $R0 < 1$. Low- and high-temperature values are the low and high 5% of the historical climate series in the area.

and faster (slower) developmental periods ($P < 0.04$ for mortality; $P < 0.02$ for development). However, contributions of transovarial and nonsystemic transmission routes to viral circulation did not change significantly ($P = 0.42$) under the scenarios of temperature. These estimated values of high or low temperatures had an impact on the viral transmission rates affecting the life processes of the tick vector.

Viral circulation was mainly supported by transovarial transmission and transmission from and to new competent reservoir hosts. The nonsystemic transmission route had a small contribution to virus dynamics. As $R0$ values increased, the contribution of transovarial transmission also increased (Fig. 1d). The contribution of transovarial

transmission tended to be higher towards southern latitudes, without a clear pattern across a longitudinal gradient (Fig. 1e).

Analysis of model biological parameters

The effect of variations in the critical biological parameters of the model, H (fraction of tick blood meals on infective hosts), i (duration of host infection), R (efficiency of transovarial transmission), θ (efficiency of tick-to-tick transestadial transmission) and $P + Q$ (transmission from hosts to ticks and *vice versa*) was evaluated. Increments in all these parameters increased $R0$, and their decrements produced the consequent decrease in $R0$.

However, these parameters made different contributions to virus circulation, the sensitivity of the system and the relative changes in $R0$ across the geographical range of the study. A decrease in H highlights the relative importance of both transovarial and nonsystemic transmission routes that became the dominant routes in virus circula-

tion. In turn, values of $R0$ were slightly lower under this scenario. Combined transovarial and nonsystemic transmissions accounted for near 100% of total contributions to virus transmission at low values of H. Increases in H resulted in a highest contribution of the nonsystemic transmission route alone to virus circulation (Fig. 2a).
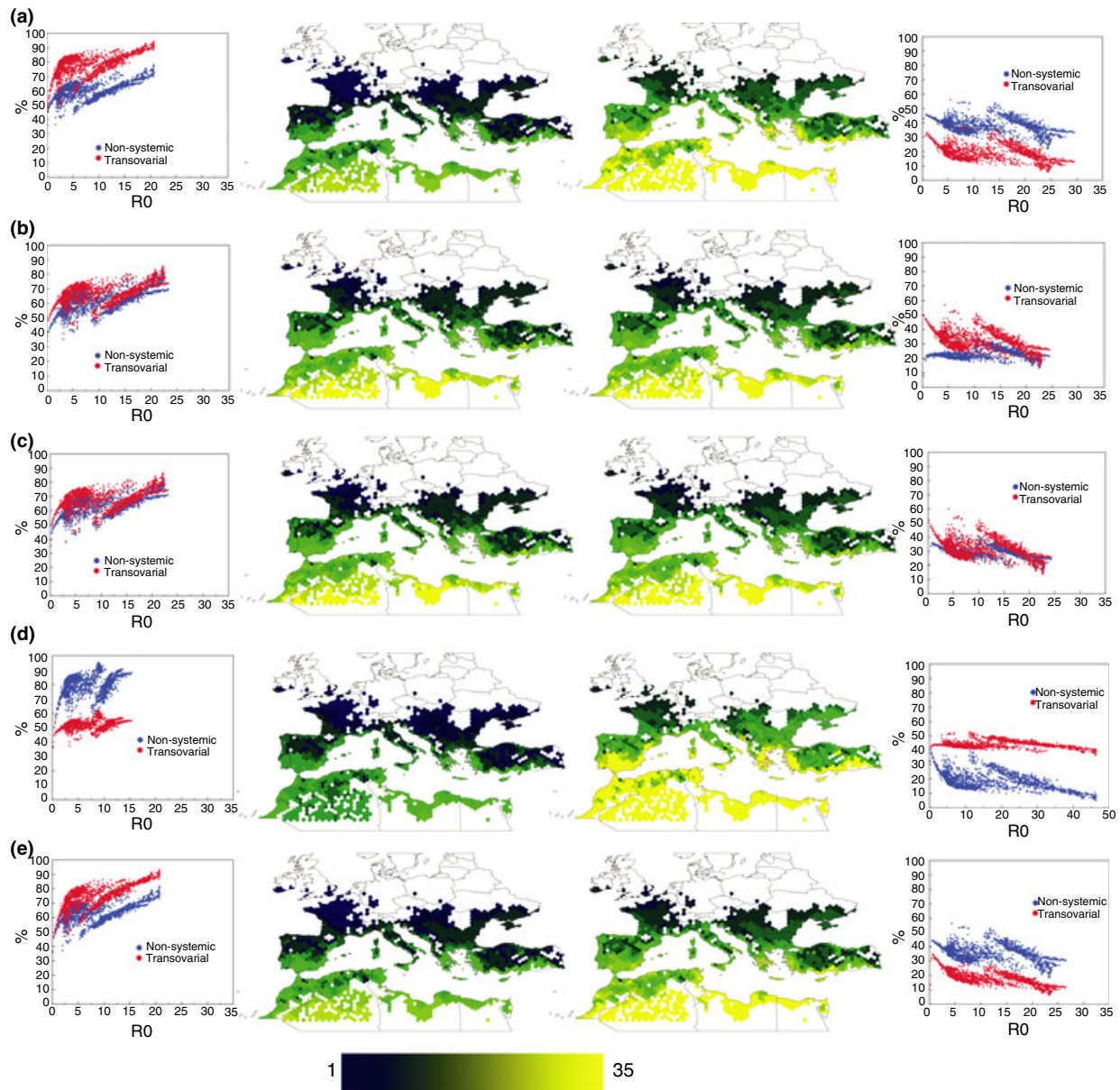
Figure 2 Changes in $R0$ geographical distribution and in the relative contribution of different virus transmission routes according to variations in biological parameters of the model. Chart and map at left and right display the model runs with low and high values of the corresponding biological parameters, respectively. $R0$ values are displayed in a gradient from dark ($R0 = 1$) to light ($R0 = 35$). (a) Fraction of tick blood meals on hosts competent for systemic transmission, $H = 0.1$ (left) and $H = 0.9$ (right). (b) Duration of systemic infection in days, $i = 1$ (left) and $i = 20$ (right). (c) Efficiency of virus transmission from infected hosts to ticks (P) and from infected ticks to hosts (Q), P or $Q = 0.1$ (left) and P or $Q = 0.9$ (right). (d) Efficiency of virus transovarial transmission, $R = 0.1$ (left) and $R = 0.9$ (right). (e) Efficiency of tick-to-tick transmission, $\theta = 0.1$ (left) and $\theta = 0.2$ (right). (●) Non-systemic; (●) transovarial.

The increase in *i* had the effect of decreasing the contribution of both transovarial and nonsystemic transmission routes because of the increase in the contribution of the systemic transmission route. In contrast, the decrease in *i* produced an increase in both transovarial and nonsystemic transmission routes. Variations in *i* produced only slight variations in the range of $R0 \geq 1$ ($P = 0.09$, Fig. 2b). Variations in PQ affected $R0$ in a way similar to *i*. Therefore, the increase in *R* decreased the contribution of both transovarial and nonsystemic transmission routes because of the increase in the contribution of the systemic transmission route. A decrease in *R* produced an increase in both transovarial and nonsystemic transmission routes. The simulated changes in *R* accounted only slight variations in the range of $R0 \geq 1$ ($P = 0.18$, Fig. 2c). The changes in *R* alone produced the highest effect on the $R0$ values ($P < 0.001$) with a twofold increase in some areas (Fig. 2d). This increase may switch the $R0$ from <1 to >1 in some areas. A large decrease in *θ* had a high impact by decreasing $R0$ values over the entire geographic range of the study ($P < 0.01$). Using a low efficiency of virus transovarial transmission at high *θ* increased the impact of the nonsystemic transmission route, which accounted for up to 85% of the total contribution to virus circulation. With increasing *θ*, the nonsystemic transmission route made the most significant contribution to the increase in the $R0$ values (Fig. 2e). The nonsystemic transmission route was dominant with low efficiencies of transovarial transmission, accounting for over 90% of the viral circulation in some cases. How-

ever, the transovarial transmission route supported around 50% of viral circulation at high *R* values.

In summary, the system was very sensitive to small changes in transovarial transmission, stressing its contribution to the virus circulation. The system had a low sensitivity to changes in *θ*, with moderate sensitivity to temperature changes (Fig. 3) but showed a high sensitivity to changes in *H* only in the highest range of $R0$ values, supporting the importance of systemic transmission only under some epidemiological conditions.

Discussion

The finding of CCHFV in south-western Europe (Estrada-Peña *et al.* 2012b) suggested that the presence of the virus together with the wide distribution of *H. marginatum*, its main vector, in the Mediterranean basin, represent a risk for virus circulation in the region (Gale *et al.* 2011). Our study linked a process-driven tick life cycle model with projection matrices and elasticity analysis as an improvement towards the characterization of the potential endemic area for CCHFV in western Palearctic. Concerns exist about the existence of suitable climate and host abundance conditions to cause an emerging CCHF epidemic in this region (Gale *et al.* 2011). We ignore basic epidemiological parameters for the transmission of CCHFV and how changes in transmission rates among ticks and competent reservoir hosts affect virus circulation and geographic range. The model showed how changes in climate and virus transmission rates affect
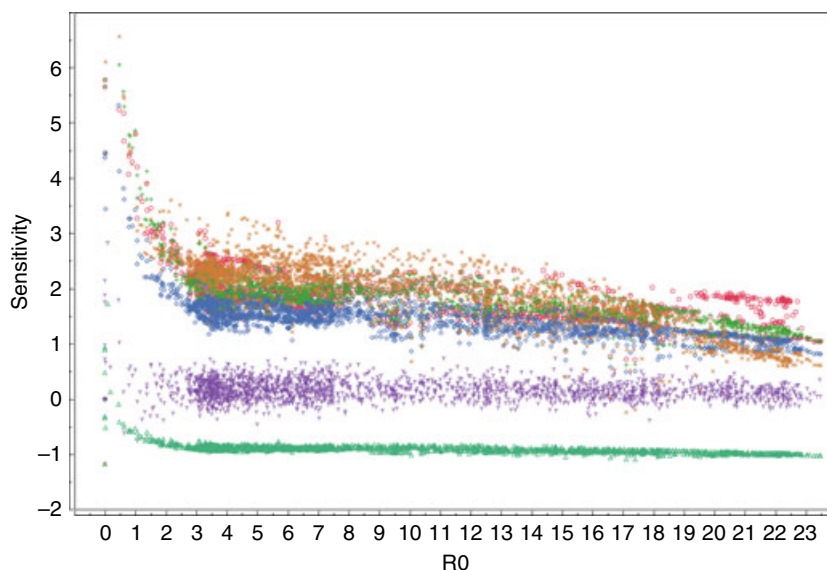
Figure 3 Sensitivity of the model to changes in the basic parameters governing the biotic features of Crimean–Congo haemorrhagic fever virus (CCHFV) transmission (*H, I, P, Q, R, θ*) and temperature (*T*) with respect to $R0$ values. (○) *H*; (+) *I*; (◇) *PQ*; (ϒ) *T*; (×) *R*; (△) *θ*.

CCHFV distribution in the region and how virus transmission routes are affected by these changes.

Two main results were obtained from our simulations, (i) transovarial transmission is essential for CCHFV circulation and (ii) temperature changes affect tick vector seasonal development and mortality rates, thus promoting both higher $R0$ values and a larger geographical range for viral circulation. However, the effects of temperature alone would not change the relative importance of transovarial transmission on CCHFV circulation. The effects of climate on the epidemiology of CCHFV have been discussed elsewhere (Gray *et al.* 2009). It is often claimed that warmer temperatures would promote epidemics in the context of the ongoing debate about the impact of climate on tick-borne pathogens (Ergonul and Whitehouse 2007; Maltezou and Papa 2010). However, it was previously shown that climate did not change significantly in the areas of Turkey where the recent and still ongoing CCHF epidemics occur (Estrada-Peña *et al.* 2011). Our model showed that a rise in temperature might lead to the expansion of the area with endemic potential for CCHFV. Higher temperatures had a direct impact on faster tick development rates and thus a decrease in density-independent mortality, which in turn affected parasite loads on hosts. A secondary impact of higher temperatures is that oviposition would take place well before autumn, improving the survival of developing eggs (Emelianova 2006) and likely promoting the geographical spread of the tick. However, changes in tick seasonality because of climate alone did not promote large changes in $R0$ or in the contribution of transovarial transmission as the main route for virus circulation. Temperature values used here were the upper and lower 5% statistical limits of the historical series of weather in the region, within the normal temperature variability in the region and thus considered as the most realistic scenario for the analysis.

CCHFV produces persistent infections that last almost for the entire tick life with epidemiological significance for perpetuation of the virus in nature (Kondratenko 1976; Shepherd *et al.* 1989). CCHFV transovarial transmission has been demonstrated under both natural and experimental conditions, and the epidemiological significance of these findings is well recognized (Kondratenko *et al.* 1970). The decrease in the efficiency of transovarial transmission had the single largest effect on the decrease in mean $R0$ values over the studied region. The model was very sensitive to small changes in transovarial transmission rates, further supporting the hypothesis that this transmission route has the main contribution to the maintenance of active virus foci. All data suggest that transovarial transmission together with high systemic transmission between hosts and ticks are the most effective ways for virus circulation in nature. Therefore, it is proposed that higher CCHFV prevalence rates in ticks are expected in sites where adult ticks concentrate on infected ungulates, and where particular climate conditions favour the survival of the tick's eggs that became infected by transovarial transmission. The strong contribution of transovarial transmission on CCHFV circulation has been overlooked in other reports, because it was considered to be dependent only on those ticks feeding on humans, which are accidental hosts (Matser *et al.* 2009). A tick-pathogen system cannot exclusively rely on the outcome from an accidental host. While clinically affected, humans have no role on virus transovarial transmission in the field because the contribution of adult ticks feeding on ungulates is much larger.

As expected, every change indirectly promoting higher transovarial transmission rates increased $R0$ values. However, the model showed that nonsystemic transmission plays a minor role in the circulation of CCHFV. Our model did not explicitly consider host density as affecting the dynamics of the system, and we modelled parasitic loads by climate-driven tick survival rates and a negative binomial distribution. With this approach, ticks have a fixed mortality rate, which may affect more or less individuals according to the activity rates driven by climate. This is assumed to model tick infestations when the seasonal patterns of tick abundance are estimated and mortality rates of the many hosts supporting populations of immature ticks are unknown (Poulin 1993). We considered that the use of climate-driven tick activity rates and fixed density-derived tick mortality rates, while not totally free of criticisms, is a realistic way to characterize the impact of the other parameters of the model.

We acknowledged that local processes, which depend on climate and host abundance, might be relevant only under particular conditions. These processes must be incorporated into models of spread after full characterization of tick-dependent processes. Linking a tick life cycle model with recent developments in NGM helped to assess these epidemiological features in a large territory. These findings open an interesting perspective for spatial models that incorporate host rates and seasonality, therefore allowing the use of tick and host phenology. The simulations conducted here showed that warmer temperatures have a positive effect on CCHFV spread into northern latitudes in the western Palearctic by affecting tick vector survival rates. However, the high impact of virus transovarial transmission did not change under realistic scenarios, therefore suggesting that other factors such as hosts for immature ticks have a low impact on the local maintenance and spread of infective foci. The abundance of domestic and wild ungulates that are hosts for adult ticks

together with an increasingly suitable habitat for tick survival may be the key factors for CCHFV spread.

In conclusion, a scenario of increased temperature is compatible with the spread of CCHFV in the western Palearctic, because expansion of the habitat suitable for tick vectors and thus the area available for virus circulation. This scenario would affect the whole region and will increase virus circulation in sites where high tick populations may already exist. However, a warmer climate will not affect the relative contribution of the main virus transmission routes. The relative importance of transovarial route of transmission from ticks to ticks may be greatly exacerbated by uncontrolled movements and significant increase in ungulate hosts for adult ticks.

Acknowledgements

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1 Supplementary information regarding the building and validation of the model.

Table S1 Tick-related parameters.

Table S2 Pathogen-related parameters.