A mathematical model for Crimean-Congo haemorrhagic fever: tick-borne dynamics with conferred host immunity

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\section{ABSTRACT}
Crimean-Congo haemorrhagic fever (CCHF) is a highly contagious tick-borne disease that impacts many countries in parts of Africa, Europe, Asia, and the Middle East. Outbreaks are episodic, but deadly. Due to the highly contagious nature of this disease, suspected cases are taken extremely serious, with very strong control measures implemented almost immediately. It is primarily those living on farms, livestock workers, and medical workers who are at risk. The virus responsible for CCHF is transmitted asymptomatically and transiently to livestock, and symptomatically to humans. The fatality rate in human cases can be very high. The number of methods and directions of viral transmission is large, including tick-to-tick, tick-to-livestock, tick-to-human, livestock-to-tick, livestock-to-human, and human-to-human. We model CCHF using a deterministic system of nonlinear differential equations. This compartment model allows us to analyse threshold parameters and equilibria describing the magnitude and progression of cases of the disease in a hypothetical outbreak.

\section{1. Introduction}
Crimean-Congo haemorrhagic fever (CCHF) has been recognized at least since the Second World War, when Soviet troops who were re-occupying part of the Crimean peninsula fell ill with the fever in alarming numbers [16]. The symptoms of CCHF in humans are quite severe. As Bente \textit{et al.} [1] describe:

In the 1944 Crimean outbreak, hospitalized patients showed a sudden onset of fever, accompanied by weakness, headache and muscular pains, vomiting, marked hyperemia of the face and oropharynx, a haemorrhagic rash with development of ecchymoses and bleeding from the nasopharynx, gastrointestinal tract and other sites.

In addition there is some anecdotal evidence of CCHF from centuries earlier [16]. CCHF has had small but deadly outbreaks in a number of countries in parts of Africa, Europe, Asia, and the Middle East [1].
To give a sense of the scope of modern occurrences of CCHF, we note that in the years 2002–2012 roughly 6300 CCHF cases were reported in Turkey, now considered by some to be the ‘epicentre’ of CCHF [1]. Bente et al. [1] summarize the episodic, but dangerous, nature of disease outbreaks. A handful of countries report more than 50 CCHF cases per year to the World Health Organization [1]. In the summer of 2013, there were six cases in Uganda, two of which resulted in death [15].

The virus responsible for CCHF is carried primarily by certain kinds of hard ticks of the genus *Hyalomma* [10]. This is evidenced by the close correlation between the geographic distribution of CCHF cases and the geographic distribution of this kind of tick [3]. There is also a clear seasonal component to the spread of CCHF, due to the tick life cycle and the impact of higher temperatures. The predominance of cases occur in the spring and summer [10], when ticks at both immature and adult stages of the life cycle seek hosts for blood meals [1].

Ticks transmit the virus to other ticks both vertically (parent to offspring) and horizontally (to one another while feeding on the same animal, and from males to females while mating) [7]. Once infected, ticks remain infected for life [1]. Various livestock, while not contracting CCHF, are able to become infected with the virus through contact with infected ticks at various stages in the tick life cycle. In fact, different sized animal species are the predominant hosts at different stages in the tick life cycle, with smaller species serving as hosts in the earlier tick life cycle stages and larger species serving as hosts for adult ticks [10]. Here, we are using the term ‘livestock’ to include all of the larger (non-human) animal species since our model considers only the adult life stage for the ticks. We are modelling the tick–livestock–human system over one season.

The infection in livestock is transient [1]; this infection is also short-lasting, persisting for about a week and apparently not harming the livestock in any way. Infected livestock can infect susceptible ticks which are feeding on them. However, it is believed that humans are ‘dead end’ hosts for the virus and do not transmit the disease to livestock or to ticks [1]. Infected ticks can infect humans. Infected livestock also can infect humans, through the butchering and farming process. Finally, humans can infect humans through various forms of contact with blood and bodily fluids due to, among other things, insufficiently safe barrier medical practices in hospitals [10]. It is, therefore, primarily farmers, livestock workers, and medical workers who are at risk for CCHF.

For humans who become infected, the fatality rate can be quite high. Whitehouse [16] quotes an overall average fatality rate of 30%, though in Turkey the fatality rate is about 5% [1]. Outbreaks of CCHF are taken very seriously. The US Centers for Disease Control in fact lists the CCHF virus as a severe biosafety level-4 pathogen, and there has been some limited talk of the potential dangers of the use of the CCHF virus in bio-terrorism [16]. Bente et al. [1] call CCHF ‘the most important tick-borne viral disease of humans’.

Much work has been carried out on the mathematical modelling of tick-borne diseases. Some of this work is focused on a specific tick-borne disease such as Lyme disease, while some models are kept more general (see, e.g. the metapopulation model in [5] and the global dynamics model in [6]). Several general biological/epidemiological reviews of CCHF have been written (see, e.g. [1, 3, 10, 16]), and many specialized scientific papers have been published on various aspects of CCHF (more than 500 articles by 1979, according to [1]). On the mathematical side of things, there have been a small number of papers focused specifically on CCHF. For example, Poisson regression has been applied to CCHF.
data from Iran [9]. The basic reproduction number has been examined in reference to the important differences between modelling diseases spread by insect-borne parasites and modelling those spread by tick-borne parasites, with specific reference to CCHF [4]. Various biological and mathematical considerations have been explored for the mathematical modelling of CCHF [2]. Here, we model CCHF by means of a deterministic system of nonlinear differential equations. The dynamics of CCHF are explored in the three populations of human, tick, and livestock. This may be broken down as needed to look at the in-depth propagation of the disease between subgroups.

2. Model formulation and analysis

In this section, a model for the transmission of CCHF between ticks, humans, and livestock is designed and analysed. The causes of infection include tick-to-tick, tick-to-livestock, livestock-to-tick, tick-to-human, livestock-to-human, and human-to-human contact. With the fact that outbreaks often occur due to unexpected circumstances such as the introduction of livestock into a new region or weather conditions that cause ticks to be especially active in seeking hosts, we assume that no population reaches equilibrium levels faster than the other.

In the tick population, we consider SI dynamics since the tick remains infected for life [1], while in the livestock and human populations we consider SIR dynamics. Let the total population of ticks be $N_1$, the total population of livestock be $N_2$, and the total population of humans be $N_3$. Ticks may be born either infected or uninfected, since some proportion of infected female ticks transmit the disease to their offspring [1]. We model infection in livestock as conferring complete immunity to future infection. While the immunity may in fact be lengthy but temporary, we anticipate application of the model over short enough time periods (a single season) that the assumption of immunity should be reasonable. If these are livestock on a farm, then the mortality rate may primarily be due to slaughter rather than natural mortality. We consider all these populations to be constant during the outbreak by assuming equal recruitment and death rates since the outbreak usually takes place in a short period of time during which changes in the populations are trivial. The recruitment and death rates for the tick population are set to $\mu_1$, with corresponding rates set to $\mu_2$ for the livestock population, and to $\mu_3$ for the human host population.

Let the susceptible tick population be denoted by $X_1$ and the infected tick population be denoted by $Y_1$, with $N_1 = X_1 + Y_1$. Vertical transmission in the ticks is assumed by setting a proportion $p$ of the newborn ticks to be infected. Thus, the rate of recruitment into the susceptible tick population is $\mu_1 (N_1 - pY_1)$, with the rate of recruitment into the infected tick population given by $\mu_1 pY_1$. A more detailed treatment would consider the life stages of the ticks and differentiate between vertical transmission through an infected female tick and vertical transmission through an infected male tick (should such transmission be possible). A susceptible tick can be infected through co-feeding with an infected tick or from an infected livestock. Successful tick-to-tick transmission of infection depends on the rate of co-feeding between susceptible tick and infected tick, the probability of infection, and the proportion of infectious ticks.

Let $\sigma_{11}$ be a measure of the tick feeding rate and $\beta_{11}$ be a measure of the co-feeding transmission probability. For the tick population, the proportion of infectious ticks is $Y_1/N_1$. Therefore, the force of infection for tick-to-tick transmission is $\sigma_{11} \beta_{11} Y_1 / N_1$. By setting
\( \sigma_{11} \beta_{11} \) to \( \gamma_{11} \), the force of infection from tick-to-tick interactions is given by \( \gamma_{11} Y_1 / N_1 \). The second means of infection for the tick is from infected livestock. Here, we let \( \sigma_{12} \) be a measure of the tick biting rate on livestock, and \( \beta_{12} \) be a measure of the livestock-to-tick transmission probability. Successful transmission also depends on the fraction of the host population that is infected. Thus, the force of infection for livestock-to-tick transmission will be given by \( \gamma_{12} Y_2 / N_2 \), where we have let \( \gamma_{12} = \sigma_{12} \beta_{12} \).

We model infection in livestock as conferring complete immunity to future infection. While the immunity may in fact be lengthy but temporary, we anticipate application of the model over short enough time periods (a single season) that the assumption of immunity should be reasonable. Using similar definitions as for livestock-to-tick transmission, the force of infection for tick-to-livestock transmission is given by \( \gamma_{21} Y_1 / N_2 \) and the force of infection for tick-to-human transmission is given by \( \gamma_{31} Y_1 / N_3 \). These transmissions are due to ticks feeding on livestock and to ticks biting humans, respectively.

For livestock-to-human and human-to-human transmission, let \( \sigma_{32} \) be a measure of livestock–human interaction rate and let \( \sigma_{33} \) be a measure of human–human interaction rate. Let \( \beta_{32} \) be a measure of livestock-to-human transmission probability and let \( \beta_{33} \) be a measure of human-to-human transmission probability. By setting \( \gamma_{32} = \sigma_{32} \beta_{32} \) and \( \gamma_{33} = \sigma_{33} \beta_{33} \), the forces of infection for livestock-to-human and for human-to-human transmissions are, respectively, \( \gamma_{32} Y_2 / N_3 \) and \( \gamma_{33} Y_3 / N_3 \). These transmissions are due to human contact with livestock in the farming and butchering process, and to human contact with infected humans in the course of regular daily life or at the hospital.

If we define \( q_2 \) and \( q_3 \) as the livestock and human rates of recovery from the infection, then the model describing the transmission of CCHF between ticks, livestock, and humans is given by

\[
X_1' = \mu_1 (N_1 - p Y_1) - \gamma_{11} \frac{X_1}{N_1} Y_1 - \gamma_{12} \frac{Y_2}{N_2} X_1 - \mu_1 X_1,
\]

\[
Y_1' = \mu_1 p Y_1 + \gamma_{11} \frac{X_1}{N_1} Y_1 + \gamma_{12} \frac{Y_2}{N_2} X_1 - \mu_1 Y_1,
\]

\[
X_2' = \mu_2 N_2 - \gamma_{21} \frac{X_2}{N_2} Y_1 - \mu_2 X_2,
\]

\[
Y_2' = \gamma_{21} \frac{X_2}{N_2} Y_1 - q_2 Y_2 - \mu_2 Y_2,
\]

\[
Z_2' = q_2 Y_2 - \mu_2 Z_2,
\]

\[
X_3' = \mu_3 N_3 - \gamma_{31} \frac{X_3}{N_3} Y_1 - \gamma_{32} \frac{X_3}{N_3} Y_2 - \gamma_{33} \frac{X_3}{N_3} Y_3 - \mu_3 X_3,
\]

\[
Y_3' = \gamma_{31} \frac{X_3}{N_3} Y_1 + \gamma_{32} \frac{X_3}{N_3} Y_2 + \gamma_{33} \frac{X_3}{N_3} Y_3 - q_3 Y_3 - \mu_3 Y_3,
\]

\[
Z_3' = q_3 Y_3 - \mu_3 Z_3.
\]

Each parameter \( \gamma_{ij} \) is an efficacious contact rate per population type \( i \) individual per unit time with population type \( j \) individuals. In the case of ticks and livestock, the mode of contact allows for the exchange of virus in either direction (livestock to tick, \( \gamma_{12} \); or tick-to-livestock, \( \gamma_{21} \)). We are careful to use the term ‘efficacious contact rate’ for these parameters. For example, not every bite received by a susceptible livestock from an infected tick will
result in infection in the livestock. Similarly, not every bite made by a susceptible tick to an infected livestock will result in infection in the tick. Bente et al. [1] comment that 'A feeding tick may remain attached for several weeks, enhancing the likelihood of virus transmission from an infected tick to its host, or from a viremic host to its feeding, virus-naive ticks.' It is important to note that the human-to-human contact rate $\gamma_{33}$ is entirely dependent on the early detection of infection and subsequent effectiveness of barrier medical procedures. With early detection, the value of $\gamma_{33}$ can be brought down almost to 0. However, with inadequate barrier medical procedures and inadequate detection of infection, the value of $\gamma_{33}$ can be quite high. Ergonul [3], for example, reports that 'In one hospital outbreak, it was reported that 8.7% of health-care workers who were exposed to infected blood and 33% of those who had a needlestick injury developed the disease'. Furthermore, when asymptomatic cases go unrecognized, individuals may unintentionally continue to infect those around them during the infection period. The livestock-to-human contact rate depends on use of safety equipment in the farming industry. Ideally, the value of $\gamma_{32}$ can be brought down almost to 0 as well. However, with poor farming safety practice as in many rural areas where CCHF outbreaks occur, the value of $\gamma_{32}$ also can be quite high.

Since our model assumes equal birth and mortality rates, the total population sizes $N_1$, $N_2$, and $N_3$ are constant. This assumption is made because a CCHF outbreak usually takes place over a short period of time (again, we are considering one season). To analyse the model, we rescale system (1). This is done by letting $x_1 = X_1/N_1$, $y_1 = Y_1/N_1$, $x_2 = X_2/N_2$, $y_2 = Y_2/N_2$, $z_2 = Z_2/N_2$, $x_3 = X_3/N_3$, $y_3 = Y_3/N_3$, and $z_3 = Z_3/N_3$. The quantities $x_i$, $y_i$, and $z_i$ represent the proportions of population type $i$ that are susceptible, infected, and recovered, respectively. Thus, we have $x_1 + y_1 + 1 = 1$, $x_2 + y_2 + z_2 = 1$, and $x_3 + y_3 + z_3 = 1$. Under this rescaling and after simplifying by using $x_1 = 1 - y_1$, $x_2 = 1 - y_2 - z_2$, and $x_3 = 1 - y_3 - z_3$, system (1) becomes

$$y_1' = -(1 - p)\mu_1 y_1 + (\gamma_{11} y_1 + \gamma_{12} y_2) (1 - y_1),$$
$$y_2' = m_{21} \gamma_{21} y_1 (1 - y_2 - z_2) - q_2 y_2 - \mu_2 y_2,$$
$$z_2' = q_2 y_2 - \mu_2 z_2,$$
$$y_3' = (m_{31} \gamma_{31} y_1 + m_{32} \gamma_{32} y_2 + \gamma_{33} y_3) (1 - y_3 - z_3) - q_3 y_3 - \mu_3 y_3,$$
$$z_3' = q_3 y_3 - \mu_3 z_3.$$

In the scaled system (2), the constants $m_{21} = N_1/N_2$, $m_{31} = N_1/N_3$, and $m_{32} = N_2/N_3$ are, respectively, tick-to-livestock, tick-to-human, and livestock-to-human population ratios. Successful transmission from any direction between any two populations involves a constant number of bites or contacts per unit time, independent of the population density of the host population [12, 14].

It is clear that system (2) has a disease-free equilibrium, $(0, 0, 0, 0, 0)$. Since $x_1 = 1 - y_1$, $x_2 = 1 - y_2 - z_2$, and $x_3 = 1 - y_3 - z_3$, all solutions of $y_1, y_2, z_2, y_3$, and $z_3$ that are biologically meaningful for this system lie in the interval $[0, 1]$.

When the disease-free equilibrium does not exist, an endemic equilibrium exists which is given by

$$y_1^* = y_1^* + \frac{y_1^* (\mu_1 (1 - p) - \gamma_{11} (1 - y_1^*)))}{\gamma_{12} (1 - y_1^*)^2},$$
$$z_2^* = \frac{q_2 y_2^*}{\mu_2},$$
\[ m_{31} \gamma_{31} y_1^* + m_{32} \gamma_{32} y_2^* + \gamma_{33} y_3^* = \frac{(q_3 + \mu_3)y_3^*}{(1 - y_3^* - (q_3 y_3^*/\mu_3))}, \quad \text{and} \quad z_3^* = \frac{q_3 y_3^*}{\mu_3}. \]  

It is observed from Equation (3) that \( y_1^*, z_2^*, \) and \( z_3^* \) are always positive since we are only concerned with solutions for which all endemic equilibrium levels are between 0 and 1. Therefore, to prove existence of the endemic equilibrium point in Equation (3), it suffices to show that both \( y_2^* \) and \( y_3^* \) are always positive. From \( y_2^* = y_1^*(\mu_1(1-p) - \gamma_{11}(1-y_1^*))/\gamma_{12}(1-y_1^*), \) we see that \( y_2^* \) is positive if and only if \( y_2^* = y_1^*(\mu_1(1-p) - \gamma_{11}(1-y_1^*))/\gamma_{12}(1-y_1^*) > 0. \) That is, if

\[
y_1^* > 1 - \frac{\mu_1(1-p)}{\gamma_{11}}.
\]  

Similarly, to prove that the solutions to the equation \( m_{31} \gamma_{31} y_1^* + m_{32} \gamma_{32} y_2^* + \gamma_{33} y_3^* = \frac{(q_3 + \mu_3)y_3^*}{(1 - y_3^* - q_3 y_3^*/\mu_3)} \) are positive, it suffices to show that \( \gamma_{33} y_3^* - (q_3 + \mu_3)y_3^* > 0, \) implying that

\[
\frac{\gamma_{33}}{q_3 + \mu_3} > 1 \quad \text{for} \quad y_3^* \ll 1.
\]  

Therefore, we conclude that the endemic equilibrium exists if Equations (4) and (5) are satisfied.

In order to discuss the stability of both the disease-free and the endemic equilibria, we compute the basic reproductive number \( R_0, \) using the method described by Van den Driessche and Watmough [13]. In this case

\[
R_0 = \max[R_h, R_d],
\]  

where \( R_h \) and \( R_d \) will be defined later on in the section. The Jacobian matrix evaluated at the disease-free equilibrium is given by

\[
J(0, 0, 0, 0, 0) = \begin{pmatrix}
\gamma_{11} - (1 - p)\mu_1 & \gamma_{12} & 0 & 0 & 0 \\
0 & -(q_2 + \mu_2) & 0 & 0 & 0 \\
m_{21} \gamma_{21} & 0 & -\mu_2 & 0 & 0 \\
m_{31} \gamma_{31} & m_{32} \gamma_{32} & 0 & -q_3 - (q_3 + \mu_3) & 0 \\
0 & 0 & 0 & q_3 & -\mu_3 \\
\end{pmatrix}
\]  

(7)

It is clear from Jacobian (7) that \(-\mu_2, -\mu_3, \) and \( \gamma_{33} - (q_3 + \mu_3) \) are eigenvalues. These three eigenvalues are all real-valued and negative provided \( \gamma_{33} < (q_3 + \mu_3) \) or

\[
R_h = \frac{\gamma_{33}}{q_3 + \mu_3} < 1.
\]  

(8)

The remaining two eigenvalues are obtained from the two-by-two matrix given by

\[
\begin{pmatrix}
\gamma_{11} - (1-p)\mu_1 & \gamma_{12} \\
m_{21} \gamma_{21} & -(q_2 + \mu_2)
\end{pmatrix}
\]  

(9)

The eigenvalues corresponding to the reduced Jacobian matrix in Equation (9) are given by

\[
\lambda_{4,5} = \frac{1}{2} \left[ -\gamma_{11} + (1-p)\mu_1 + q_2 + \mu_2 \right] \pm \sqrt{(\gamma_{11} - (1-p)\mu_1 + q_2 + \mu_2)^2 + 4\gamma_{12} m_{21} \gamma_{21}}.
\]
Note that the term under the square root sign is positive for all meaningful sets of parameter values. The condition that will make both $\lambda_4$ and $\lambda_5$ be negative and guarantee stability of the disease-free equilibrium is if

$$-\left[-\gamma_{11} + (1 - p)\mu_1 + q_2 + \mu_2\right] + \sqrt{(\gamma_{11} + (1 - p)\mu_1 + q_2 + \mu_2)^2 + 4\gamma_{12}m_{21}\gamma_{21}} < 0.$$  

Using Equation (8) at the point when $R_h = 1$, we can determine the critical efficacious infection rate of human-to-human transmission. When $R_h = 1$ we have $\gamma_{33}^{\text{critic}} = q_3 + \mu_3$. This result is summarized in the following proposition:

**Proposition 2.1:** The critical level of efficacious infection rate of human-to-human transmission $\gamma_{33}^{\text{critic}}$ is equal to the net rate at which humans move out of the infected state.

Note in system (2) that the first three equations (for ticks and livestock) are decoupled from the final two equations (for humans). As a first step in the analysis, we study the decoupled tick–livestock subsystem to get an understanding of the dynamics of the disease within the tick and livestock populations. The resulting system has disease-free and endemic equilibrium levels, which can be proved to be stable. Note further that the basic reproductive number associated with human-to-human transmission was already obtained, and the tick-to-livestock dynamics are not influenced by the human population. Later on, we shall derive similar expressions that describe the dynamics of CCHF between livestock and humans, and between ticks and humans. For now, we discuss the tick and livestock transmission. The basic reproductive number is defined as the average number of secondary infections produced by an infected animal in a completely susceptible livestock population. It thus provides a threshold such that the disease-free equilibrium is locally asymptotically stable when the basic reproductive number is less than unity and is unstable when this quantity exceeds unity. Using the next generation approach described by Van den Driessche and Watmough [13], the basic reproductive number for the decoupled tick–livestock subsystem, considering vertical transmission as a new infection, is

$$R_{tl} = R_{t} + \sqrt{R_{t}^2 + R_{l}},$$

where

$$R_t = p + \frac{\gamma_{11}}{\mu} \quad \text{and} \quad R_{l} = \frac{\gamma_{12}m_{21}\gamma_{21}}{(\mu_2 + q_2)\mu_1}.$$  

A related threshold quantity $Q_{tl}$ is given by $Q_{tl} = R_t + R_l$. This type of threshold quantity is given, for example, in [8] in the context of the modelling of citrus grove infection by the bacterial disease known as citrus greening. Due to the additive form of $Q_{tl}$, it is nicely interpreted termwise as a sum of three terms, $p$ for tick-to-tick vertical transmission, $\gamma_{11}/\mu_1$ for tick-to-tick horizontal transmission, and the usual vector–host reproduction number $R_t$ for tick-to-livestock and livestock-to-tick transmission.

Perhaps one would wish to determine how to eliminate CCHF from a population. One way of doing so is to find the proportion of the population needed to be kept infection free.
by applying all control strategies in place. We do this by applying a method as in Roberts and Heesterbeek [11] to system (2) by first determining the next generation matrix

$$
K = FV^{-1} = \begin{pmatrix}
\frac{\gamma_{11}}{(1-p)\mu_1} & \frac{\gamma_{12}}{\mu_2 + q_2} & 0 \\
\frac{m_{21}\gamma_{21}}{(1-p)\mu_1} & 0 & 0 \\
\frac{m_{31}\gamma_{31}}{(1-p)\mu_1} & \frac{m_{32}\gamma_{32}}{\mu_2 + q_2} & \frac{\gamma_{33}}{\mu_3 + q_3}
\end{pmatrix}.
$$

(11)

As stated in Roberts and Heesterbeek [11], for an infection that has multiple hosts that concentrate without loss of generality on host type 1, the cumulative number of infected hosts of type 1 that result in this process, as a result of chains of infection that link one or more of host types 2 to \(n\) (3 in our case) without another infected host of type 1 being allowed to reproduce, is denoted by

$$
T_1 = e^TK(I - (I - P)K)^{-1}e,
$$

(12)

where \(I\) is the \(n \times n\) identity matrix, \(P\) is the projection matrix, defined by \(P_{11} = 1, P_{ij} = 0\) when \(i \neq 1\) or \(j \neq 1\), and \(e\) is a unit vector. Applying this to our system shows that

$$
T_1 = \frac{\gamma_{11}}{(1-p)\mu_1} + \frac{\gamma_{12}m_{21}\gamma_{21}}{(1-p)(q_2 + \mu_2)\mu_1} = R_{th} + R_{l1}.
$$

(13)

Thus, the infection will be eliminated if a proportion greater than

$$
1 - \frac{1}{T_1} = \frac{(1-p)(R_{th} - 1) + R_{l}}{(1-p)R_{th} + R_{l}}
$$

(14)

of tick-to-tick transmissions plus the tick-to-livestock and livestock-to-tick infections can be prevented. It is difficult, however, to prevent or control CCHF infection in animals and ticks as the tick–animal–tick cycle usually goes unnoticed and the infection in domestic animals is usually not apparent [17]. Furthermore, the tick vectors are numerous and widespread, so tick control with acaricides (chemicals intended to kill ticks) is only a realistic option for well-managed livestock production facilities.

We now consider relationships between \(R_{tl}, Q_{tl}, T_1\), and stability of the disease-free equilibrium.

**Theorem 2.2: Tick–livestock–human stability.**

(i) The threshold quantity \(R_{tl} < 1\) if and only if the threshold quantity \(Q_{tl} < 1\).

(ii) If \(\max[R_h, Q_{tl}] < 1\), then the disease-free equilibrium \((0,0,0,0,0)\) is locally asymptotically stable.

We omit the proof, which involves straightforward but somewhat tedious algebra.
We can determine critical levels of interaction parameters in $Q_{tl}$ for infection transmission between ticks and livestock. When $Q_{tl} = 1$, we have

$$Q_{tl} = 1 = \frac{1}{2} \left( p + \frac{\gamma_{11}}{\mu_1} \right) + \sqrt{\frac{1}{4} \left( p + \frac{\gamma_{11}}{\mu_1} \right)^2 + \frac{\gamma_{12} \gamma_{21}}{(1-p)(q_2+\mu_2)\mu_1}}.$$ 

Therefore,

$$1 - \frac{1}{2} \left( p + \frac{\gamma_{11}}{\mu_1} \right) = \sqrt{\frac{1}{4} \left( p + \frac{\gamma_{11}}{\mu_1} \right)^2 + \frac{\gamma_{12} \gamma_{21}}{(1-p)(q_2+\mu_2)\mu_1}},$$

which is equivalent to

$$1 - \left( p + \frac{\gamma_{11}}{\mu_1} \right) = \frac{\gamma_{12} \gamma_{21}}{(q_2+\mu_2)}.$$ 

To obtain meaningful analysis, we will look at two possibilities: either there is no transmission of infection between ticks and livestock in at least one of the directions ($\gamma_{12} = 0$ or $\gamma_{21} = 0$), or there is no tick-to-tick transmission ($\gamma_{11} = 0$).

If $\gamma_{12} = 0$ or $\gamma_{21} = 0$, then $\gamma_{11} = (1-p)\mu_1$. When $\gamma_{11} > (1-p)\mu_1$, the disease prevails; the disease dies out otherwise. From this we make the following proposition:

**Proposition 2.3:** For successful transmission between ticks, the infection rate must exceed the rate of recruitment into the susceptible population of ticks.

If no infection takes place between ticks by ticks (that is when $\gamma_{11} = 0$), we have

$$\gamma_{12} \gamma_{21} = \frac{(1-p)(q_2+\mu_2)}{m_2}.$$ 

This result is summarized in the following proposition:

**Proposition 2.4:** When $\gamma_{11} = 0$, the model reduces to the classic vector–host model.

The threshold criteria we have obtained for $R_h$, $R_{tl}$, and $Q_{tl}$ provide insight into the spread of the CCHF virus among ticks, livestock, and humans. In particular, the form for $Q_{tl}$ indicates that the spread of infection among ticks and livestock would not develop into an epidemic if low efficacious contact rates were paired with a low vertical transmission rate for ticks, high death rates for ticks and livestock (with the tick death rate probably much more important), and a high recovery rate for livestock.

In outbreaks of CCHF, many of the human cases are due to tick-to-human transmission [1]. One survey in Turkey found that 'Of all the reported cases, 68.9% had a history of tick-bite or tick contact and 84.1% were seen in the months of May, June, and July’ (when ticks are most active) [18]. In what follows, we ignore livestock-to-tick transmission by assuming $\gamma_{12} = 0$. We assume that humans who become infected with CCHF are removed from the general population at some rate and treated under quarantine. Determination of whether these treated individuals die from the disease or recover is dependent on the
efficacy of treatment measures and is thus outside the scope of this model. We focus on the tick dynamics in Equation (2)

\[ y_1' = -(1 - p)\mu_1 y_1 + \gamma_{11} y_1 (1 - y_1). \]

To solve for the tick endemic equilibrium level, we set

\[ \gamma_{11} y_1^2 + [(1 - p)\mu_1 - \gamma_{11}]y_1 = 0. \]

The equilibrium proportions \((x_1^*, y_1^*)\) are given by the infection-free equilibrium \((1, 0)\) and the endemic equilibrium \(x_1^* = (1 - p)\mu_1/\gamma_{11}, y_1^* = (\gamma_{11} - (1 - p)\mu_1)/\gamma_{11}\). Here, the endemic equilibrium is biologically meaningful \((0 \leq x_1^* \leq 1, 0 \leq y_1^* \leq 1)\) if and only if \(\gamma_{11} > (1 - p)\mu_1\). We can now define \(R_{th}\), the basic reproduction number between ticks and humans, as

\[ R_{th} = \frac{\gamma_{11}}{(1 - p)\mu_1}. \]  \hspace{1cm} (16)

If \(R_{th} < 1\), there is no biologically meaningful endemic equilibrium. In the absence of a biologically meaningful endemic equilibrium, the infection-free equilibrium \((1, 0)\) is asymptotically stable. Otherwise, there is an asymptotically stable endemic equilibrium given by

\[ \left( \frac{1}{R_{th}}, \frac{R_{th} - 1}{R_{th}} \right). \]

This implies that in the absence of a tick–livestock–tick cycle, the ticks on their own can only maintain an endemic level of the virus if the impact of horizontal tick-to-tick transmission is greater in magnitude than the impact of tick births/deaths paired with vertical transmission. When \(R_{th} > 1\), we expect to see an asymptotically stable endemic equilibrium in the tick population. Therefore, if we assume that the tick population has reached endemic equilibrium, it can be shown that the human population will have some endemic level of infection greater than 0. That is, if there is some endemic level of tick infection greater than zero, the reality of a non-zero probability that some humans will be bitten by ticks and become infected with CCHF leads to the inevitability of a human endemic level of infection.

### 3. Discussion

In the model presented here, we provided a deterministic system for CCHF that explores the tick–livestock dynamics, the tick–human dynamics, and the full tick–livestock–human dynamics. We saw that the stability of disease-free equilibria and of endemic equilibria is dependent on the values of critical combinations of parameters; see, e.g. \(R_{th}\) as defined in Equation (8).

We determined a basic reproductive number \(R_0 = \max\{R_{l}, R_{ht}\}\) in Equation (6). We found that the disease-free equilibrium is more likely to be locally asymptotically stable when the rate of vertical transmission of the virus in tick populations is low, when tick birth and death rates are high, when livestock birth and death rates are high, when livestock recovery rates are high, when human death and recovery rates are high, and when
efficacious contact rates are low. Note that it is the extreme human-to-human contagiousness that results in the increasing likelihood of the stability of the disease-free equilibrium as human death and recovery rates increase.

In the tick–livestock model, we found that the disease-free equilibrium is more likely to be locally asymptotically stable when the rate of vertical transmission of the virus in tick populations is low, when tick birth and death rates are high, when livestock birth and death rates are high, when livestock recovery rates are high, and when efficacious contact rates are low; see, e.g. $R_{dt}$ and $T_1$ as defined in Equations (10) and (13), respectively.

In outbreaks of CCHF the majority of the human cases appear to be due to tick-to-human transmission of the disease. In a special case of this model that assumed no livestock-to-tick transmission, we found a reproductive number $R_{th}$ governing the stability of the infection-free equilibrium for ticks; see Equation (16). This equilibrium is more likely to be locally asymptotically stable when the rate of vertical transmission of the virus in tick populations is low, when tick birth and death rates are high, and when efficacious contact rates between ticks are low. With any level of livestock-to-tick transmission, an endemic equilibrium for tick infections is present and is locally asymptotically stable. With inclusion of the human hosts dynamics, we found that in virtually all biologically meaningful scenarios an endemic equilibrium for human host infections exists and is asymptotically stable.

In real outbreaks of CCHF, strong response measures should be (and generally are) taken quickly to ensure that outbreaks do not spread to epidemic levels. We saw this quick, strong response in summer 2013 in Uganda, involving a national task force that went into action almost immediately about suspicion and then confirmation of CCHF. Control measures include very strict barrier medical policies, as well as very strict quarantining of associates of infected persons. These response measures drastically impact parameter values. While there is the possibility of the development of CCHF outbreaks of epidemic proportions, it would seem that to date control measures have adjusted parameter values enough to prevent wide-scale CCHF epidemics. However, if control measures become too lax, or are not implemented soon enough, a true epidemic can develop. We cannot emphasize too strongly the importance of continued vigilance in watching for CCHF-type symptoms and responding extremely strongly when CCHF cases are found.

The work presented here gives preliminary insight into the types of impact that various changes in parameter values can have on the behaviour of the tick–livestock–human CCHF system. We have also provided a starting point for further modelling work on this important and deadly disease.

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References

[1] D.A. Bente, N.L. Forrestor, D.M. Watts, A.J. McAuley, C.A. Whitehouse, and M. Bray, Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity, Antivir. Res. 100 (2013), pp. 159–189.

[2] B. Cooper, Mathematical modeling of Crimean-Congo hemorrhagic fever transmission, in Crimean-Congo Hemorrhagic Fever: A Global Perspective, O. Ergonul and C. Whitehouse, eds., Springer, New York, 2007, pp. 187–203.

[3] O. Ergonul, Crimean-Congo haemorrhagic fever, Lancet Infect. Dis. 6 (2006), pp. 203–214.

[4] A. Estrada-Pena, L. Jameson, J. Medlock, Z. Vatansever, and F. Tishkoba, Unraveling the ecological complexities of tick-associated Crimean-Congo hemorrhagic fever virus transmission: A gap analysis for the Western Palearctic, Vector Borne Zoonotic Dis. 12 (2012), pp. 743–752.

[5] H.D. Gaff and L.J. Gross, Modeling tick-borne disease: A metapopulation model, Bull. Math. Biol. 69 (2007), pp. 265–288.

[6] H. Gomez-Acevedo, Global stability in a model for diseases transmitted by ixodid ticks, Can. Appl. Math. Q. 11 (2003), pp. 81–92.

[7] J.P. Gonzalez, J.L. Camicas, O. Cornet, O. Faye, and M.L. Wilson, Sexual and transovarian transmission of Crimean-Congo haemorrhagic fever virus in Hyalomma Truncatum ticks, Res. Virol. 143 (1992), pp. 23–28.

[8] K. Jacobsen, J. Stupiansky, and S. Pilyugin, Mathematical modeling of citrus groves infected by Huanglongbing, Math. Biol. Sci. Eng. 10 (2013), pp. 705–728.

[9] E. Mostafavi, S. Chinikar, S. Bokaei, and A. Haghdoot, Temporal modeling of Crimean-Congo hemorrhagic fever in Eastern Iran, Int. J. Infect. Dis. 17 (2013), pp. e524–e528.

[10] S. Oncu, Crimean-Congo hemorrhagic fever: An overview, Virol. Sin. 28 (2013), pp. 193–201.

[11] M.G. Roberts and J.A.P. Heesterbeek, A new method for estimating the effort required to control an infectious disease, Proc. R. Soc. Lond. B 270 (2003), pp. 1359–1364.

[12] J.C. Thomas, Epidemiologic Methods for the Study of Infectious Diseases, Oxford University Press, Oxford, 2001.

[13] P. Van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, J. Math. Biosci. 180 (2002), pp. 29–48.

[14] J.H. Vandermeer and D.E. Goldberg, Population Ecology. First Principles, Princeton University Press, Princeton, NY, 2003.

[15] J.F. Wamala, I. Makumbi, M. Ope, R. Mugabe, C.L. Okot, T. Shoemaker, S. Balinandi, L. Nyakarahuka, and D. Ndumu, Crimean-Congo Hemorrhagic Fever (CCHF) Outbreak in Uganda – 2013, East African Community Integrated Disease Surveillance Network Bulletin. Accessed November 11, 2013. Available at http://eaidsnet.eac.int/crimean-congo-hemorrhagic-fever-cchf-outbreak-in-uganda-2013/.

[16] C.A. Whitehouse, Crimean-Congo hemorrhagic fever, Antivir. Res. 64 (2004), pp. 145–160.

[17] Crimean-Congo Haemorrhagic Fever, accessed June 25, 2015. Available at http://www.who.int/mediacentre/factsheets/fs208/en/.

[18] G.R. Yılmaz, T. Büzgan, H. Irmak, A. Safran, R. Uzan, M.A. Cevik, and M.A. Torunoglu, The epidemiology of Crimean-Congo hemorrhagic fever in Turkey, 2002–2007, Int. J. Infect. Dis. 13 (2009), pp. 380–386.