Epidémiol. santé anim., 1997, 31-32

MODELLING THE TRANSMISSION DYNAMICS OF *COWDRIA RUMINANTIUM* : SUPPORTING THE CASE FOR ENDEMIC STABILITY

O'Callaghan C.[1,2], Medley G.[1], Peter T.[3], Perry B.[4]

Cet article décrit la formulation du modèle de transmission dynamique de Cowdria ruminantium où les variables « réponse » sont les manifestations cliniques (heartwater disease) et la mortalité. Le modèle présenté n'est pas un modèle de simulation, il s'agit de plusieurs séries d'équations différentielles déterministes. Nous présentons la structure du modèle en mettant l'accent sur les hypothèses biologiques sous jacentes et les résultats préliminaires. L'épidémiologie des maladies transmissibles par les tiques accepte le concept de stabilité endémique (situation dans laquelle agent et vecteur coexistent en absence de maladie clinique). La compréhension actuelle des inter-relations permet uniquement une classification descriptive des différentes catégories épidémiologiques. Le modèle développé dans notre étude permet de démontrer et de mieux explorer le concept de stabilité endémique. Ce modèle a été également utilisé pour évaluer la stratégie vaccinale selon trois scénarios : i) à l'état d'équilibre de la maladie, ii) dans le cas d'une épidémie et iii) en situation préventive avant l'introduction du vecteur. D'autres variables ont été considérées dans un modèle dynamique amélioré comme les caractéristiques du vaccin, la fréquence de vaccination, le niveau de la couverture vaccinale, le groupe ciblé et la stratégie vaccinale.

INTRODUCTION

Heartwater, caused by the rickettsial organism *Cowdria ruminantium* and transmitted by ticks of the genus *Amblyomma*, is considered to be the most important tick-borne disease of cattle in southern Africa, and is second only in importance to East Coast fever (theileriosis) in eastern Africa. This paper describes the formulation of a transmission dynamic model for *C. ruminantium* in which the clinical manifestations of infection, namely heartwater disease and death, are the outcomes of interest and are reported as functions of relative tick challenge.

MODEL FRAMEWORK

Herein we provide an outline of the model developed and the corresponding mathematical details. The model is deterministic in nature and is based on our current understanding of the underlying biological processes. It incorporates a single primary host population in which there are six mutually exclusive categories, based on infection status, as follows, (with the corresponding mathematical symbol highlighted):

Susceptible to infection; x - These are naive animals that have not been exposed to *C. ruminantium* previously, are susceptible to infection and at risk of developing fatal disease. Calves born to dams in this group are themselves susceptible after a period of innate protection.

Acutely infected but will survive; y - Following infection of a susceptible animal, an acute infection develops during which the probability of infecting ticks is relatively high. Clinical signs, if they occur, will occur in this period, although the definition of this group is dependent on the rate of decay of infectiousness to ticks, rather than the outward signs of infection. The animals in this category recover to become carriers of infection.

Acutely infected but will die; s - On infection of a susceptible animal, a proportion will die from heartwater. On average, death occurs at a rate faster than the rate at which animals recover, thus reducing the opportunity of these animals to infect ticks, although they are assumed to be as infectious as those which recover. Death of the animal is the principal cost of heartwater and hence it is the main indicator used in the model. These animals are assumed not to reproduce, nor are they subject to non-heartwater mortality.

Carriers; z - Those animals that recover from acute infection are deemed to be carriers; they are able to infect ticks but are immune to further disease. They may become re-infected, but this does not alter their infectiousness. Carriers may also arise from infection of an animal that is protected from disease by i) maternal factors, ii) innate factors, iii) vaccination, or directly by vertical transmission. Calves born to carrier dams may be

[1] Department of Biological Sciences, University of Warwick, Coventry, United Kingdom, CV4 7AL
[2] Department of Population Medicine, University of Guelph, Guelph, Ontario, Canada, N1G 2W1
[3] UF/USAID/SADC Heartwater Research Project, P.O. Box CY 551, Harare, Zimbabwe
[4] International Livestock Research Institute, P.O. Box 30709, Nairobi, Kenya

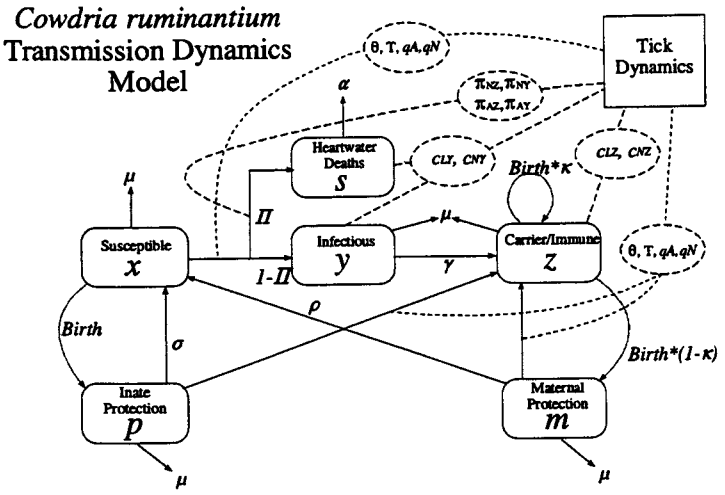

Figure 1

infected vertically (in which case the calves are immediately carriers), but will always have protection from disease given by maternal factors even if not actually infected.

Maternal factor protected; ***m*** - Calves that have been born to carrier dams, but were not vertically infected, are assumed to be protected against disease but not infection. If they are infected during this period of protection calves become carriers without passing through a period of acute infection or risking death. If calves are not exposed during this period of protection, they become fully susceptible.

Age specific protection; ***p*** - Calves born to susceptible animals have an innate protection which lasts for a shorter period of time than that derived from maternal factors. Infection during this period will also result in the carrier status, without passing through an acute phase. No exposure during this period will result in the calf becoming susceptible.

The host population is given the nominal value of unity (1.0), thus making the sub-populations represent the proportions in each stage. Consequently, the model outcome units, where appropriate, are *per head of cattle.* The tick population is considered only in respect of the proportion of attachments that are by infectious ticks and the total attachment rate. Only nymphae and adults are able to transmit infection, while the proportion of individuals that die is determined by the source of the infection. We assume that infections from adult ticks are more likely to result in death than infections from nymphae (although there is no distinction between adults by gender), and that infections from ticks that were infected by animals going through an acute infection are more likely to kill than infections from ticks that were infected by carriers. Potential for accumulation of infective dose is not accounted for in the current model. The parameters of the model are supplied in Table 1 and the model framework is summarised in Figure 1.

The details supplied in the text produce the following series of deterministic time-delayed differential equations:

$$\frac{dm}{dt} = \beta(t)z(1-\kappa) - m[\mu+\rho+\lambda(t)]$$

$$\frac{dp}{dt} = \beta(t)(1-z) - p[\mu+\sigma+\lambda(t)]$$

$$\frac{dx}{dt} = \rho m + \sigma p - x[\lambda(t)+\mu]$$

$$\frac{dy}{dt} = [1-\Pi(t)]\lambda(t)x - y(\gamma+\mu)$$

$$\frac{ds}{dt} = \Pi(t)\lambda(t)x - s\alpha$$

$$\frac{dz}{dt} = \beta(t)(1-x)\kappa + \gamma y + \lambda(t)[m+p] - z\mu$$

$$\beta(t) = \mu(x+y+z+m+p)+\alpha s$$

$$\lambda(t) = T\left(q_A\left[K_{Ay}+K_{Az}\right]+\theta q_N\left[K_{Ny}+K_{Nz}\right]\right)$$

$$\Pi(t) = \frac{1}{\theta q_N q_A}\left\{\frac{\left[\pi_{Ny}r_{Ly}+\pi_{NZ}r_{Lz}\right]\theta q_N}{r_{Ly}+r_{Lz}} + \frac{\left[\pi_{Ay}r_{Ny}+\pi_{Az}+r_{Nz}\right]q_A}{r_{Ny}+r_{Nz}}\right\}$$

$$\frac{dK_{Ny}}{dt} = (\omega_N+\eta_N)\left\{r_{Ly}(t-\phi_L) - K_{Ny}\right\}$$

$$\frac{dK_{Nz}}{dt} = (\omega_N+\eta_N)\left\{r_{Lz}(t-\phi_L) - K_{Nz}\right\}$$

$$\frac{dK_{Ay}}{dt} = (\omega_A+\eta_A)\left\{r_{Ny}(t-\phi_N) - K_{Ay}\right\}$$

$$\frac{dK_{Az}}{dt} = (\omega_A+\eta_A)\left\{r_{Nz}(t-\phi_N) - K_{Az}\right\}$$

$$r_{Ly}(t) = c_{Ly}[y+s]$$

$$r_{Lz}(t) = c_{Lz}z$$

$$r_{Ny}(t) = K_{Ny}x + c_{Ny}[y+s]$$

$$r_{Nz}(t) = K_{Nz}x + c_{Nz}z$$

With the following function definitions:

l(t) the rate of infection which is the sum of infection rates from the different types of tick weighted by the relative nymphal attachment rate, probabilities of infection and the adult tick attachment rate.

r(t) the proportion of ticks (larvae and nymphae) entering the next questing stage (nymphae and adults) that were infected by acutely infected and carrier animals (y, s and z). The equation for r_N recognises that infected adults come essentially from two sources: infected nymphae that fed on uninfected hosts, and nymphae that became infected from infectious hosts.

b(t) the birth rate. For simplicity this has been initially assumed to be equal to the death rate from causes other than heartwater plus heartwater deaths, in order to keep the host population constant.

P(t) the proportion of animals that die from heartwater on infection. Noting that only susceptible animals can be killed, the proportion dying is a combination of the lethality of the different instars and sources of infection (i.e. nymphae and adults infected by acute and carrier animals), the prevalence of infection within each type of tick and relative infection efficiency of nymphae and adults. The parameters are defined in Table 1 where rate parameters are given in days. A rate of 1/n implies that the average duration in the stage is n days.

QUANTIFICATION OF ENDEMIC STABILITY

We have taken the highest tick attachment rate (observed in field studies in heartwater endemic areas of Zimbabwe) of 0.5 adults per day (= TAR_{MAX}), which results in 99.9% carrier prevalence. We then decreased this rate stepwise and made a comparative analysis of the equilibria attained. Noting the log scale on the x-axes, Figure 2a shows that the proportion of animals that are carriers and susceptible essentially following the results of Medley *et al.* (1993) in that a very small attachment rate can still produce a reasonable proportion of carriers, partly due to vertical transmission (here 50%) and the long duration of the carrier state. However, heartwater incidence (Figure 2b) and case fatality (Figure 2c) exhibit maxima at intermediate attachment rates due to a combination of factors. Principally, these are that i) reducing the attachment rate (from TAR_{MAX}) by a factor 100 only increases the proportion susceptible to approximately 30% and ii) increasing incidence concomitantly changes the lethality of infections due to the proportion of ticks that are infected by acutely infected animals.

These results provide the first model-based reproduction of the principle of "endemic stability" whereby relatively high rates of vector challenge are counter-intuitively associated with very low rates of disease. Although tick-borne disease epidemiology has been associated with the concept of endemic stability (specifically defined as a situation in which host, agent and vector coexist in the virtual absence of clinical disease), the current understanding of the various inter-relationships involved has to-date allowed only descriptive classifications of epidemiological categories. Perry and Young (1995) provide an overview of these epidemiological states with respect to theileriosis, and document the variations in disease incidence and case-fatality rates observed under increasing levels of tick challenge. The patterns they report, based on experience and observation, are remarkably similar to those generated by the current model, supporting the contention that endemic stability simply describes a set of circumstances on a continuum of epidemiological states. Perhaps more importantly, this may be an inherent characteristic of the transmission dynamics of many tick-borne diseases.

While the model requires further validation and assessment, it does provide a mechanism through which the processes that contribute to endemic stability can be investigated. In addition, a preliminary version has been utilised in an assessment of possible vaccination strategies under three scenarios: i) at equilibrium with respect to heartwater, ii) in the face of an epidemic and iii) prophylactically prior to vector introduction. Additional variables considered in this revised dynamic model include vaccine characteristics (e.g. duration of immunity), the frequency of vaccination, the level of vaccination coverage and the appropriate target group.

Symbol	Meaning	Value
μ	host death rate	1/1100
γ	rate of recovery from infectiousness	1/20
T	adult tick attachment rate	0.5
θ	relative nymphal attachment rate	10
κ	proportion of vertical infection in carrier births	0.5
ρ	rate of loss of maternal protection	1/30
σ	rate of loss of innate protection	1/10
Λ	rate of loss of vaccine protection	NA
α	death rate from heartwater	1/15
π_{Nz}	case fatality of infections from nymphae infected by carriers	0.1
π_{Ny}	case fatality of infections from nymphae infected by acutes	0.2
π_{Az}	case fatality of infections from adults infected by carriers	0.3
π_{Ay}	case fatality of infections from adults infected by acutes	0.4
$\omega_N+\eta_N$	host finding and death rate or questing nymphae	1/50
$\omega_A+\eta_A$	host finding and death rate of questing adults	1/50
ϕ_L	moulting delay for larvae-nymph	30
ϕ_N	moulting delay for nymph-adult	60
c_{Ly}	proportion of larvae feeding on acutes that become infected	0.5
c_{Lz}	proportion of larvae feeding on carriers that become infected	0.01
c_{Ny}	proportion of nymphae feeding on acutes that become infected	0.8
c_{Nz}	proportion of nymphae feeding on carriers that become infected	0.1
q_N	probability that an infectious nymph infects a host	0.8
q_A	probability that an infectious adult infects a host	0.9

Table 1

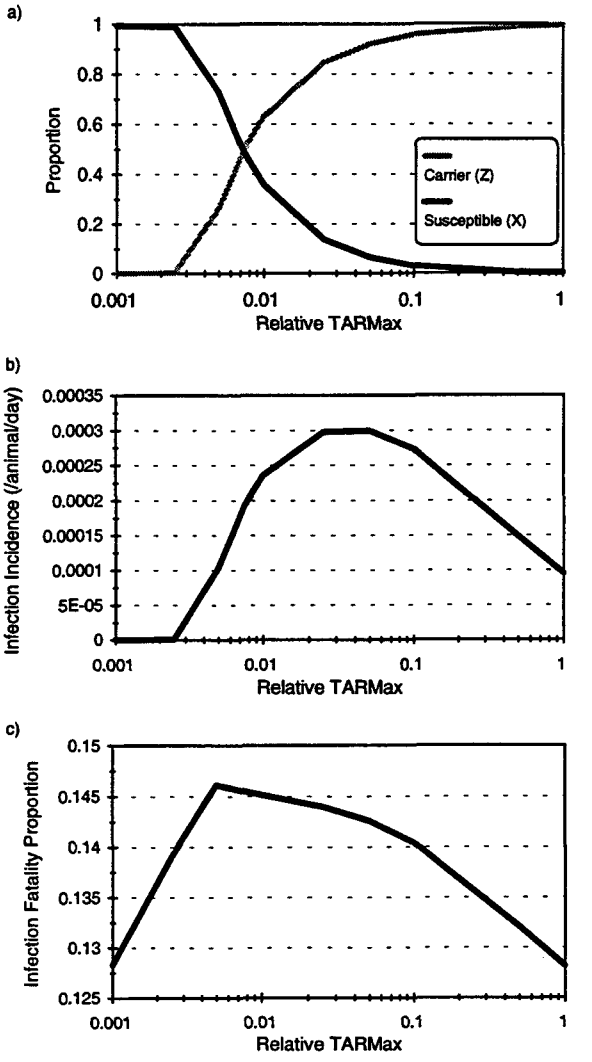

Figure 2

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