Evaluation of a nematode (*Capillaria hepatica* Bancroft, 1893) as a control agent for populations of house mice (*Mus musculus domesticus* Schwartz and Schwartz, 1943)

H.I. McCALLUM *

**Summary:** Sudden, large-scale infestations of house mice (*Mus musculus domesticus*) occur irregularly in the cereal-growing regions of Australia, resulting in substantial economic losses. Mathematical modelling has been used to evaluate the use of the liver nematode *Capillaria hepatica* as a potential agent for the biological control of mouse populations. The models suggest that *C. hepatica* is unlikely to be successful as a single-release control agent; instead, the parasite would need to be released when it becomes apparent that an outbreak is likely. Stage-structured models, including time delays and seasonal mouse demographic parameters, suggest that the parasite may be successful as a control agent, provided it can be introduced into the mouse population at least one year before an outbreak occurs. The optimum time for introduction is in summer or autumn. Some generalisations of this work are discussed. A parasite which affects fecundity alone is unlikely to be a good control agent, because it will destabilise the host population. Macroparasites may be unable to spread sufficiently rapidly to control sudden rises in vertebrate populations.

KEYWORDS: Biological control – Mathematical modelling – Mice – Parasites.

**INTRODUCTION**

“Mouse plagues” or eruptions in populations of the house mouse (*Mus musculus domesticus* Schwartz and Schwartz, 1943) occur on average every seven to nine years in the cereal-growing regions of south-eastern Australia, resulting in substantial economic losses (14). At present, no satisfactory means of control is available; no rodenticide is currently registered for in-crop use in Australia.

The potential of the liver nematode *Capillaria hepatica* Bancroft, 1893 as a biological control agent is currently being investigated. *C. hepatica* has a life cycle unique among helminths of mammals. The eggs are not released directly into the environment, but are deposited in the liver of the host mouse. Transmission can occur only through ingestion of the infected liver by another animal, after which potentially infectious eggs are released in the faeces of the predator or scavenger. In mice, transmission is thought to occur primarily through necrophagy and cannibalism (18). Studies on laboratory mice indicate that the parasite may both increase mortality and decrease fecundity (15).

* Department of Zoology, University of Queensland, St Lucia, QLD 4072, Australia.
C. hepatica is endemic in urban areas of Australia, where it has been reported from house mice and two species of introduced rat (Rattus rattus and R. norvegicus). In non-urban conditions, it has been reported from only three species of Australian native mammal, all of which were from the same rain-forest in northern Queensland. This restricted host and geographic range is probably due to ecological barriers to transmission (17). C. hepatica does not occur in the cereal-growing regions where mouse plagues occur (13).

Mathematical modelling has been integral in the evaluation of C. hepatica as a biological control agent. In this paper, experience with C. hepatica is used as an example to discuss the role of modelling in assessing the potential of parasites as biological control agents. Models may have two roles:

- Models are valuable before experimentation commences, to indicate the most critical aspects of host and parasite biology, on which experimentation should be concentrated. Frequently, the process of model construction itself, with the need for formal description of the basic interactions in the life cycle, leads to important directions for research. Initial models must be simple and general, as they are constructed before detailed information becomes available.

- A successful model should be able to predict the qualitative nature of the interaction, and possibly provide some quantitative predictions. Such a model is likely to be more complex than the initial models.

**INITIAL MODELS**

A basic model for the C. hepatica-mouse interaction was constructed along the lines developed by Anderson and May (1, 10). Details are presented elsewhere (9, 16). The most important modification to the models presented by Anderson and May is that the parasite is transmitted only upon the death of its host. This destabilises the host-parasite interaction. If the parasite is the only constraint on host population growth, diverging oscillations occur until either parasite or host becomes extinct. If there are other density-dependent constraints on host population growth, the parasite may maintain host populations below the disease-free equilibrium but there are liable to be recurrent parasite outbreaks, with resultant host population crashes. These results suggest that a parasite capable of surviving host death may cause local extinction of either itself or the host, and may therefore not be a suitable "release and forget" biological control agent.

While these simple models are ideal for indicating general patterns of behaviour, substantial problems occur because the age-structure of host and parasite is neglected. C. hepatica would have to be released on a "tactical" basis in particular regions, when weather conditions indicate that a mouse plague may be imminent (see 14 for a discussion of prediction of mouse plagues). For this reason, the long-term equilibrium behaviour is of less interest than the critical question of whether parasite numbers can build up sufficiently to have an impact on the mouse population before a full-blown plague occurs. The various developmental delays for mouse and parasite are clearly of fundamental importance here. Less obviously, time delays make it extremely difficult to establish the parameters for a non-delayed model, even given good biological information.

Accordingly, a second series of models was developed (9), using a stage-structured approach (7). This enables the realism of a simulation model to be combined with some
of the analytic tractability of a conventional differential equation model. For example, $H_T$, the threshold host population below which the parasite cannot become established in the host population, can be obtained explicitly from the stage-structured equations as follows:

$$H_T = \frac{\mu_4/\lambda}{\delta \gamma \mu_2 / (\mu_2 + \mu_6) - 1} \tag{equation 1}$$

where:

$$\frac{\mu_4/\lambda}{\text{death rate of infective stages}} = \frac{\text{infectivity}}{\gamma} = \text{eggs in mouse liver per egg ingested}$$

$$\mu_2 = \text{death rate of adult mice}$$

$$\mu_6 = \text{loss of eggs from mouse liver}$$

$$\delta = \text{proportion of ingested eggs which reach reproductive age}$$

The mouse population must be above $H_T$ if parasite introduction is to be successful. However, an unusual feature of this model is that, once established, the parasite may persist in host populations somewhat below $H_T$. This occurs because parasite-induced host death increases transmission efficiency. It is likely, however, that mouse density between outbreaks is very much below $H_T$, because $C. hepatica$ is absent from mice in cereal-growing regions, although it is present in urban areas of Australia (17).

Unfortunately, the utility of equation 1 is limited by the difficulty in measuring $\lambda$, the infectivity of the embryonated eggs. This value is defined per egg, per host and per unit of time, and is the rate at which hosts pick up eggs. In principle, $\lambda$ could be measured in an experiment. In practice, its measurement will be complicated by spatial heterogeneity of host and parasite and by host social behaviour, as transmission probably occurs most of all in mouse burrows.

**A SEASONAL MODEL**

Any model intended to represent the behaviour of a parasite when first introduced into a mouse population must take into account the seasonal nature of the environment (here the Australian cereal-growing regions). The age-structured model developed previously (9) has been modified so that mouse mortality and fecundity are variable seasonally, using simple trigonometric functions. The model equations are given in the Appendix.

Data on mouse survival, litter size and the proportion of mice breeding were obtained from Walpeup, a wheat-growing area in western Victoria (14; G.R. Singleton, unpublished findings). However, the survival data (based on trap recaptures) almost certainly underestimate adult survival (14). In conjunction with the fecundity data, the survival estimates do not lead to positive net population growth, even in the plague year
of 1984. Accordingly, an *ad hoc* adjustment of mortality by a factor of 0.25 was made so that population growth at the rate observed in 1984 was generated. Parameter values used in the simulations are based on the years 1983 and 1984, in which a large-scale infestation occurred.

Other parameters are as previously estimated (9). A particular problem is posed by the infectivity $\lambda$. In the non-seasonal models, this was circumvented by defining the mouse population size in units of the threshold population (i.e. a mouse population of 1 is $H_T$). A similar approach is applied here, using the definition of $H_T$ in equation 1, although the value of $H_T$ will vary cyclically as a complex function of the seasonal birth and death rates.

Some results of this model are shown in Figure 1. To be effective, *C. hepatica* would have to be introduced as early as possible into a mouse population which is suspected of potential rapid expansion. Control is achieved more quickly if the agent is introduced into mouse populations during the seasonal increase in population, rather than during the annual spring decline.

It has been speculated that seasonal variation in mouse survival rates might lead to increased efficiency of the parasite, compared with the non-seasonal model (9). This is borne out by the results of the seasonal model. Figure 2 shows that, regardless of the point in the annual cycle at which *C. hepatica* is introduced, it is effective more rapidly than in a comparable non-seasonal model.

![Graph showing population changes](image)

**FIG. 1**

Mathematical simulation of the level of mouse population following introduction of *Capillaria hepatica* at four different moments throughout the year

Each simulation commenced at day 0 (1 January) with an initial population of 1.0, which was allowed to increase parasite-free for one year so that a stable age distribution could develop (at which time, the total mouse population was 6.57); 1,000 embryonated eggs were then introduced at day 365 (a), day 455 (b), day 535 (c) or day 625 (d)
Mathematical simulation of the depression of the total mouse population following introduction of *Capillaria hepatica*

Depression is calculated as the figure for population with infection present divided by the estimated population if no infection is present; initial population was 1.0, which was allowed to increase parasite-free for one year so that a stable age distribution could develop (at which time, the total mouse population was 6.57); 1,000 embryonated eggs were then introduced at day 365; qualitatively similar results are obtained for infection introduced at day 455, day 535 or day 625.

**DISCUSSION**

These models have played an important role in the *C. hepatica* research programme, both by identifying critical population parameters and by indicating areas of potential difficulty. Using the models for guidance, direct experimentation is required to determine whether *C. hepatica* will be a successful control agent. A preliminary small-scale enclosure experiment (4) failed to demonstrate a difference between control and infected mouse populations, but some unknown factor appeared to regulate both populations at low levels. A larger-scale release currently in progress should provide a more definite indication of the practical potential of *C. hepatica* as a control agent.

Several points arise from this modelling which are of general significance for attempts to use parasites as biological control agents. First, a macroparasite which acts mainly by
decreasing fecundity destabilises the host-parasite interaction (in contrast to the stabilising effect of parasite-induced mortality) (1). As a result, local extinction is likely. On a larger scale, such parasites may persist as a result of spatial heterogeneity, while exhibiting complex and unpredictable dynamic behaviour (8). This is not necessarily a problem with house mice in Australia, as local extinction of the host is an acceptable outcome. However, extreme caution must be exercised if a fecundity-reducing parasite is considered as a control agent for a native vertebrate for which extinction must be avoided (such as the kangaroo in Australia). This problem is restricted to macroparasites: fecundity reduction by microparasites does not induce instability in the host population (2). Instability is also generated by parasites which are capable of surviving host death. However, an advantage of such a parasite (compared with one which dies with its host) is that selection pressure on the parasite is less likely to lead to a decrease in parasite virulence (and hence in efficiency as a control agent), as has apparently occurred with myxomatosis (3, 6). Of course, selection in mice to resist infection will still occur.

These results also highlight some of the difficulties to be expected if the use of macroparasites as biological control agents is considered. Although theory suggests that macroparasites may be able to regulate the abundance of hosts (1) and some empirical evidence indicates that they may either regulate host populations or substantially reduce host population growth rates (11, 12), macroparasites typically have generation times of the same order of magnitude as that of their hosts. This means that they are unlikely to be able to increase rapidly within the host population. The problem is exacerbated in C. hepatica by two factors:

- the requirement of host death for transmission effectively slows parasite life cycles down to those of the host
- since the parasite is being considered as a tactical agent to control a rapidly expanding species, the initial behaviour of the parasite following introduction is particularly important.

However, there are potential advantages in using macroparasites rather than microparasites as control agents. The most significant advantage is that a macroparasite is an immunologically more complex target than a microparasite (particularly a virus or bacterium) (5) and therefore problems of evolution of resistance (as have occurred with myxomatosis) are less likely to occur.

If macroparasites are to be considered as control agents, it is clearly necessary to weigh up these advantages and disadvantages. Modelling has an essential role to play in this evaluation process.

ACKNOWLEDGEMENTS

The author is grateful to G.R. Singleton for helpful discussions, comments on the manuscript and the provision of raw data. This work was funded by a Cooperative Research Grant from the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and the University of Queensland.

*  
  **

Résumé : Dans les régions céréalières d'Australie, des pullulations de souris grises (Mus musculus domesticus) se produisent de façon irrégulière, entraînant des pertes économiques importantes. Des modèles mathématiques ont été utilisés pour évaluer l'utilité de Capillaria hepatica, nématode hépatique, comme agent potentiel de régulation de ces populations de souris. Les modèles semblent indiquer qu'une dissémination unique de C. hepatica ne serait pas un moyen de contrôle efficace, et qu'il faudrait plutôt disséminer le parasite au moment où une pullulation est attendue. Des modèles progressifs, prenant en compte les temps de latence et les paramètres démographiques saisonniers des souris, semblent montrer que le parasite peut être efficacement utilisé comme agent de contrôle à condition d'être introduit au sein des populations de souris au moins un an avant que ne se produise la pullulation. Les meilleures saisons pour cette introduction sont l'été ou l'automne. L'auteur discute certaines généralisations de ces résultats. Un parasite qui n'agit que sur la fécondité n'est sans doute pas un bon agent de régulation biologique car il entraîne une déstabilisation au sein de la population hôte. Les macroparasites risquent de ne pas se disséminer assez rapidement pour réguler les explosions démographiques de vertébrés.


* * *

EVALUACIÓN DEL PAPEL DE UN NEMATODO (CAPILLARIA HEPATICA BANCROFT, 1893) EN EL CONTROL DE LAS POBLACIONES DE RATONES CASEROS (MUS MUSCULUS DOMESTICUS SCHWARTZ Y SCHWARTZ, 1943). - H.I. McCallum.

Resumen: En las regiones cerealistas de Australia se producen con irregularidad infestaciones en gran escala de ratones caseros (Mus musculus domesticus) que provocan pérdidas económicas importantes. Se ha recurrido a la modelización matemática para evaluar la capacidad del nematodo hepático Capillaria hepatica de servir de regulador potencial de las poblaciones de ratones. Los modelos parecen indicar que una sola diseminación de C. hepatica no permitirá el control eficaz de la infestación y que la diseminación del parásito debe hacerse cuando aparecen signos de posible infestación. Una serie de modelos progresivos, que incluyen plazos de tiempo y parámetros demográficos estacionales de los ratones, parecen indicar que la utilización del parásito para el control de infestaciones puede resultar eficaz siempre y cuando se le introduzca en las poblaciones de ratones por lo menos un año antes de que se produzca la infestación. La mejor época para dicha introducción es el verano o el otoño. El autor discute algunas generalizaciones de estos resultados. Un parásito que sólo tiene repercusiones en la fecundidad no tiene muchas probabilidades de ser un agente satisfactorio de regulación biológica porque desestabiliza la población huésped. Los macroparásitos no son probablemente capaces de diseminarse con suficiente rapidez como para controlar aumentos bruscos de las poblaciones de vertebrados.


* * *
Appendix

A seasonal model to evaluate the efficiency of *Capillaria hepatica* Bancroft, 1893 as an agent for the control of populations of house mice (*Mus musculus domesticus* Schwartz and Schwartz, 1943)

**VARIABLES**

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature mice</td>
<td>$H_1$</td>
</tr>
<tr>
<td>Mature mice</td>
<td>$H_2$</td>
</tr>
<tr>
<td>Unembryonated eggs</td>
<td>$E_1$</td>
</tr>
<tr>
<td>Embryonated eggs</td>
<td>$E_2$</td>
</tr>
<tr>
<td>Larval worms in mice</td>
<td>$W_1$</td>
</tr>
<tr>
<td>Mature eggs in livers</td>
<td>$W_2$</td>
</tr>
<tr>
<td>Proportion of mice surviving from birth to sexual maturity</td>
<td>$J$</td>
</tr>
<tr>
<td>Proportion of mice surviving through gestation</td>
<td>$Q$</td>
</tr>
<tr>
<td>Proportion of ingested eggs surviving to adulthood</td>
<td>$P$</td>
</tr>
</tbody>
</table>

**PARAMETERS**

<table>
<thead>
<tr>
<th>Symbol *</th>
<th>Definition**</th>
<th>Approximate value (time in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_1$</td>
<td>mouse maturation time</td>
<td>47</td>
</tr>
<tr>
<td>$\tau_2$</td>
<td>mouse gestation period</td>
<td>21</td>
</tr>
<tr>
<td>$\tau_3$</td>
<td>time until eggs embryonate</td>
<td>40</td>
</tr>
<tr>
<td>$\tau_4$</td>
<td>larval worm maturation time</td>
<td>30</td>
</tr>
<tr>
<td>$\mu_1(\theta)$</td>
<td>immature mouse death rate</td>
<td>seasonal</td>
</tr>
<tr>
<td>$\mu_2(\theta)$</td>
<td>mature mouse death rate</td>
<td>seasonal</td>
</tr>
<tr>
<td>$a(\theta)$</td>
<td>mouse birth rate</td>
<td>seasonal</td>
</tr>
<tr>
<td>$\beta$</td>
<td>decrement mouse birth rate per egg</td>
<td>$5.29 \times 10^{-8}$</td>
</tr>
<tr>
<td>$k$</td>
<td>parameter of negative binomial</td>
<td>0.5</td>
</tr>
<tr>
<td>$\mu_3$</td>
<td>death rate of unembryonated eggs</td>
<td>0.01</td>
</tr>
<tr>
<td>$\mu_4$</td>
<td>death rate of embryonated eggs</td>
<td>0.0054</td>
</tr>
<tr>
<td>$\mu_5$</td>
<td>death rate of larval worms</td>
<td>0.01</td>
</tr>
<tr>
<td>$\mu_6$</td>
<td>loss rate of eggs from liver</td>
<td>0.0001</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>egg ingestion rate</td>
<td>$1.82 \times 10^{-7}$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>eggs in liver per egg ingested</td>
<td>$7.7 \times 10^4$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>increment in mouse death rate per egg</td>
<td>$3.2 \times 10^{-9}$</td>
</tr>
</tbody>
</table>

* The seasonal parameter $\theta = z \tau$, where $z$ is an angular constant: $z = (2\pi)/365$

** Parameter definitions in this seasonal model vary slightly from those of the non-seasonal model referred to by equation 1
Mortality

\[ \mu_1(\theta) = (\mu_{11} + \mu_{12} \cos \theta + \mu_{13} \sin \theta) f \]  
\[ \mu_2(\theta) = (\mu_{21} + \mu_{22} \cos \theta + \mu_{23} \sin \theta) f \]  
\[ \mu_{11} = 0.02 \quad \mu_{12} = -0.00126 \quad \mu_{13} = -0.1532 \]
\[ \mu_{21} = 0.02 \quad \mu_{22} = -0.00126 \quad \mu_{23} = -0.1532 \]
\[ f = 0.40 \]

Fecundity

The seasonal component of fecundity is made up of seasonal variation in the proportion of mice breeding (fitted as a logistic model) \( pbr(\theta) \), seasonal variation in litter size \( ls(\theta) \) and a scaling parameter \( sp \) to take account of the fact that half the population is female and that reproduction occurs once every twenty-one days.

\[ ls(\theta) = a_{11} + a_{12} \cos \theta + a_{13} \sin \theta \]  
\[ pbr(\theta) = \frac{\exp (a_{21} + a_{22} \cos \theta + a_{23} \sin \theta)}{1 + \exp (a_{21} + a_{22} \cos \theta + a_{23} \sin \theta)} \]  
\[ a(\theta) = ls(\theta)pbr(\theta)sp \]  
\[ a_{11} = 6.578 \quad a_{12} = 0.777 \quad a_{13} = -1.260 \]  
\[ a_{21} = -1.438 \quad a_{22} = 1.777 \quad a_{23} = 0.5048 \]
\[ sp = 0.0238 \]

EQUATIONS

\[ \frac{dH_1}{dt} = R_1(t) - R_1(t-\tau_1)J(t) - \mu_1(t)H_1 \]  
\[ \frac{dH_2}{dt} = R_1(t-\tau_1)J(t) - \mu_2(t)H_2 - \alpha W_2 \]  
\[ \frac{dE_1}{dt} = R_2(t) - R_2(t-\tau_3)\exp(-\tau_3 \mu_3) - \mu_3 E_1 \]  
\[ \frac{dE_2}{dt} = R_2(t-\tau_3)\exp(-\tau_3 \mu_3) - \mu_4 E_2(t) - g(t) \]  
\[ \frac{dW_1}{dt} = g(t) - g(t-\tau_4)P(t) - W_1 \delta(t) \]  
\[ \frac{dW_2}{dt} = \gamma g(t-\tau_4)P(t) - W_2(t)(\mu_6 + \mu_2(t) + \alpha) - \alpha \left( \frac{k+1}{k} \right) \cdot \frac{W_2^2}{H_2} \]  
\[ \frac{df}{dt} = J\{\mu_1(t-\tau_1) - \mu_1(t)\} \]
As with most models of this type, the system is initially assumed to be empty and is then inoculated with organisms over a short period at commencement of the integration. There are three types of individual which may usefully be added: juvenile mice (inoculation rate $I_1$), mature mice (inoculation rate $I_2$) and embryonated eggs (inoculation rate $I_3$). As the system is initially assumed to be empty, the state variables for population sizes of mice and all parasite stages will be 0 at $t_0$. However, the survival variables $J$, $Q$ and $P$ will not be 0. Their initial values are:

$$J(t_0) = \exp \left\{ - \int_{t_0 - \tau_1}^{t_0} \mu_1(t) \, dt \right\} \quad (A19)$$

$$Q(t_0) = \exp \left\{ - \int_{t_0 - \tau_1}^{t_0} \mu_2(t) \, dt \right\} \quad (A20)$$

$$P(t_0) = \frac{I_2}{I_1 + I_2} \exp \left\{ - \int_{t_0 - \tau_4}^{t_0} \mu_2(t) + \mu_3 \, dt \right\} + \frac{I_1}{I_1 + I_2} \exp \left\{ - \int_{t_0 - \tau_4}^{t_0} \mu_1(t) + \mu_3 \, dt \right\} \quad (A21)$$

INITIAL CONDITIONS

As with most models of this type, the system is initially assumed to be empty and is then inoculated with organisms over a short period at commencement of the integration. There are three types of individual which may usefully be added: juvenile mice (inoculation rate $I_1$), mature mice (inoculation rate $I_2$) and embryonated eggs (inoculation rate $I_3$). As the system is initially assumed to be empty, the state variables for population sizes of mice and all parasite stages will be 0 at $t_0$. However, the survival variables $J$, $Q$ and $P$ will not be 0. Their initial values are:
REFERENCES


