Modelling the transmission dynamics of *Echinococcus granulosus* in dogs in rural Kazakhstan

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SUMMARY

Cystic echinococcosis, caused by *Echinococcus granulosus*, is an emerging disease in many parts of the world and, in particular, in eastern Europe and the former Soviet Union. This paper examines the abundance of infection of *E. granulosus* in the definitive host in southern Kazakhstan. Observed data are fitted to a mathematical model in order to decide if the parasite population is partly regulated by definitive host immunity and to define parameters in the model. Such data would be useful to develop simulation models for the control of this disease. Maximum likelihood techniques were used to define the parameters and their confidence limits in the model and the negative binomial distribution was used to define the error variance in the observed data. The results indicated that there were 2 distinct populations of dogs in rural Kazakhstan which had significantly different exposures to *E. granulosus*. Farm dogs, which are closely associated with livestock husbandry, particularly sheep rearing, had a relatively high mean abundance of 631 parasites per dog and a prevalence rate of approximately 23%. The best fit to the model indicated that there was significant herd immunity in the dog at this infection pressure. In contrast, village dogs which were more likely to be kept as pets had a much lower mean abundance of parasites of only 27 parasites per dog and a lower prevalence of 5·8%. With this village population of dogs, the best fit indicated negligible herd immunity.

Key words: *Echinococcus*, mathematical modelling, epidemiology, maximum likelihood.

INTRODUCTION

Since independence from the Soviet Union in 1991, there has been a substantial rise in the numbers of reported cases of human cystic hydatid disease caused by the larval stage of the canine tapeworm *Echinococcus granulosus* in Kazakhstan (Shaikenov, Vaganov & Torgerson, 1999*a*; Shaikenov *et al.* 1999*b*; Torgerson *et al.* 2002). This has been attributed to the change in agricultural practices, the abandonment of centralized slaughtering facilities, the increase in home slaughtering and the withdrawal of periodic compulsory anthelmintic treatment for rural dogs. The human incidence of cystic echinococcosis (CE) started to rise dramatically in about 1994 and has recently reached approximately 4 times the level seen in the latter days of the Soviet Union. The main endemic areas appear to be the south of the country and in the far north west where the annual incidence of human CE is now 10–15 cases per 100 000 (Torgerson *et al.* 2002). One of the purposes of this study was, therefore, to determine the prevalence and abundance of *E. granulosus* in different dog populations in southern Kazakhstan.

Models describing the transmission dynamics of *E. granulosus* have been developed (Roberts, Lawson & Gemmell, 1986). These models, together with data from Australia and China (Roberts *et al.* 1986; Ming *et al.* 1992*a*), suggest that there is no regulation of the parasite population by definitive host immunity. Since there is also no regulation by intermediate host immunity (Roberts *et al.* 1986; Gemmell, 1990; Ming *et al.* 1992*b*; Cabrera *et al.* 1996; Torgerson, Williams & Abo-Shehada, 1998) the parasite is normally said to be in an endemic steady state, with the basic reproduction ratio close to unity. This would make the parasite relatively amenable to control. Roberts *et al.* (1986) modelled the effect of immunity in dogs as a decrease in the asymptotic prevalence of infection when compared to dogs that did not develop immunity. Thus, old dogs would always have a higher prevalence of infection than young dogs regardless of the presence or absence of immunity. However, data concerning parasite populations in dogs, particularly in dogs of

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Fig. 1. Location of the study area in Kazakhstan (■).

different ages, is relatively sparse and a recent report (Lahmar, Kilani & Torgerson, 2001) suggested that the highest abundance and prevalence of *E. granulosus* is found in animals of a young age group with old dogs having fewer parasites and a lower prevalence. This pattern of infection is consistent with parasite-induced immunity in the host. Herd immunity, if present, could have a significant effect on the transmission dynamics. In particular, it could act as a stabilizing factor, making the parasite more difficult to control and the basic reproduction ratio would be substantially above unity. This paper also extends the models derived by Roberts *et al.* (1986) and Roberts, Lawson & Gemmell (1987) and uses surveillance data to define parameters that describe the variations in the abundance of *E. granulosus* with host age in the definitive host in southern Kazakhstan. Additionally, this paper utilizes maximum likelihood techniques with the negative binomial distribution to describe the error variance in the data to fit the data to the model. Such techniques, despite being mathematically robust, have been infrequently used in the past.

MATERIALS AND METHODS

Study area and animals

South Kazakhstan was the study area and dogs were examined in Almaty Oblast, Jambyl Oblast and South Kazakhstan Oblast (Fig. 1). In total, 2152 dogs were examined for the presence of *E. granulosus*. This consisted of 630 farm dogs and 1522 village dogs. All dogs were treated with up to 10 mg/kg arecoline hydrobromide in an aqueous solution. This induced the dogs to purge and intestinal contents were collected. Dogs that failed to purge were treated on a second occasion approximately 1 h later. A total of 606 farm dogs and 1463 village dogs successfully purged. Areas were selected at random and all dogs within the selected areas were examined. The purged material was carefully analysed in a large flat-bottomed basin. The material was repeatedly washed, parasites allowed to sediment and the supernatant removed. The numbers of *E. granulosus* parasites were carefully counted to give a total count for each dog examined. Although *E. multilocularis* also occurs in Kazakhstan (Shaikenov & Torgerson, 2002), it has a very patchy distribution and has not been previously recorded in the selected study areas. Consequently, a detailed examination of the proglottids of the parasite was not undertaken to differentiate any possible infection with *E. multilocularis*. Parasites that were morphologically consistent with *Echinococcus* were assumed to be *E. granulosus*. For some dogs with heavy infections a proportion of the purged material was examined and total worm counts were estimated from the numbers evaluated in the sample. The age of the dog was ascertained by careful questioning of the owner and, in a few cases, confirmed by a locally issued dog licence.

Analysis

From the studies of Roberts *et al.* (1986, 1987) the variation in the proportion of animals (S) susceptible to infection with *E. granulosus* (in either the definitive or intermediate host) at age t can be modelled using the equation:

$$S = \frac{1}{\gamma + ah}[\gamma + \exp\{-(\gamma + ah)t\}], \quad (1)$$

where a is a parameter influencing the rate of acquisition of immunity, h is the infection pressure in parasites per year, and γ is the rate of loss of immunity. If each dog in the population is exposed to a constant infection pressure of h parasites per

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year, these will only establish in dogs that are susceptible to infection. Dogs will also be losing parasites due to senescence at a rate that is proportional to the parasite burden. Therefore the change in the mean abundance of parasites M with age t can be modelled as:

$$\frac{dM}{dt} = hS - \mu M, \tag{2}$$

where μ is the death rate ($1/\mu$ is the parasite life-expectancy).

Therefore, by substituting (1) into (2) and solving for M, with initial condition $M=0$ when $t=0$, the variation in the numbers of parasites with age is:

$$M = \frac{ah^2}{(\gamma+ah)(\mu-\gamma-ah)} \times [\exp\{-(\gamma+ah)t\} - \exp\{-\mu t\}] + \frac{\gamma h}{\mu(\gamma+ah)}[1-\exp\{-\mu t\}]. \tag{3}$$

If there is no immunity following exposure (i.e. $a=0$) this simplifies to:

$$M = \frac{h}{\mu}[1-\exp\{-\mu t\}]. \tag{4}$$

The data were entered onto the Excel™ (Microsoft Corp, Redmond WA) spreadsheet with type of dog (farm or village), age of dog and parasite burden. Initially, the abundance of infection between village and farm dogs were first compared assuming that the animals were all from the same population. The mean abundance and negative binomial constant k were calculated by maximum likelihood techniques assuming a common mean and negative binomial constant. This was compared to the maximum likelihood value of the two populations with separate means and negative binomial constants. The 2 competing hypotheses (i.e. 1 population or 2 populations) were compared using the likelihood ratio test. This indicated a significant difference ($P<0{\cdot}0001$) so for all subsequent analyses farm dogs were analysed separately from village dogs.

The model was fitted to the data using a negative binomial likelihood function to give the probability of the number of parasites s for each observation o_i given the mean M predicted by the abundance model (equation 3 or 4).

$$Pr\{o_i=s\} = \frac{\Gamma(k+s)}{\Gamma(k)s!}\left(\frac{M}{k+M}\right)^s\left(\frac{k}{k+M}\right)^k$$

where Γ is the gamma function.

All the observations were fitted using this likelihood function and the total likelihood was:

$$\prod_{i=1}^{n} Pr\{o_i=s\}.$$

The parameter values and k values that gave the maximum likelihood were estimated using the Solver add on for Excel™ (Microsoft Corp, Redmond WA). A likelihood profile, and hence confidence intervals and probability density distributions of the parameters given the data and the model, was found by using the likelihood profile function of the Excel™ (Microsoft Corp, Redmond WA) PopTools add on (CSIRO Australia). Analysis was undertaken on each occasion assuming a different value for the negative binomial constant k for each age group and a common k value for all age groups. In addition, both data sets (village and farm dogs) were fitted to a nested model (equation 5) assuming there was no immunity in the definitive host. Likelihoods were converted to logarithms and summed to prevent calculation overflow. Confidence intervals for the actual observed data were calculated by taking the data from each group of dogs of interest and constructing a likelihood profile using the negative binomial function as the likelihood function.

Confidence bands of the variation of abundance with age were estimated by a randomization method. Briefly, once the probability distributions of the parameters were known, these were entered as user-defined distributions in Crystal Ball Software (Decisioneering Corp, Denver Colorado). One thousand random simulations, using a latin hypercube sampling technique, were run. With every simulation each parameter was picked from its distribution to estimate the abundance for each age group. The lower and upper 2·5 percentiles were used for each age group for the confidence bands.

Bayesian inference

Some of the parameters, such as the infection pressure, can only be estimated from the data. However, the life-expectancy $1/\mu$ has been suggested by experimentation. A number of studies have indicated that the life-expectancy of the infection is between 6 and 22 months (see Harris, Revfeim & Heath, 1980). In particular, studies in Uzbekistan suggested that the life-expectancy of *E. granulosus* in dogs is approximately 10 months (Aminjanov, 1975) following a single infection with 25 000 protoscolices. Thus a prior normal probability density for μ was suggested with a mean of 1·1 and standard deviation of 0·2.

To calculate the posterior distribution of the parameters given the priors, the data and the model a macro was written in Excel™ (Microsoft Corp, Redmond WA) that randomly sampled the prior value of μ across its distribution. For each random sample simulation, the likelihood was maximized to calculate the other parameters in the model. This process was repeated 5000 times. The total likelihood of the posterior distributions were calculated and a probability distribution constructed using the proportion of the total likelihood that fell within each discrete interval of the parameters, and hence the Bayesian posterior value of the parameter and

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Table 1. Maximum likelihood values of parameters and negative binomial constant for the nested model for village dogs and 95% confidence limits

Parameter	Most likely	Lower 95%	Upper 95%	Bayesian posterior median value	Lower 95%	Upper 95%
h	30·0	9·91	461	33·2	24·8	42·6
μ	0·95	0·024	13·34	1·09	0·72	1·48
k	0·00736	0·00582	0·00918	0·00736	0·00735	0·00736

confidence intervals. This is similar to the method described by Hilborn & Mangel (1997).

The Solver function in Excel™ (Microsoft Corp, Redmond, WA) sometimes converges on local rather than global minima (McCullough & Wilson, 1999). Because of this, the data were systematically analysed and included macros to start Solver from a number of different points. Thus there is a high degree of confidence that the results presented are derived from global minima.

RESULTS

The mean abundance (±95% negative binomial confidence intervals) of *Echinococcus* in farm dogs was 631 (399–1086) parasites per dog, whilst the mean prevalence (± exact 95% binomial confidence intervals) was 23% (19·8–26·6). This was a significantly greater mean abundance and prevalence than the 27 (16–53) and 5·8% (4·7–7·1) respectively in village dogs ($P<0·0001$ in each instance). Apart from the differences between farm and village dogs, there were no differences detected between abundance or prevalence from dogs in different regions.

Village dogs

The nested model (equation 4) indicated that, with the reduction in the number of parameters, the model with no host immunity was a better fit than the model which included a term for the presence of immunity ($P=0·22$ for improvement in the model with the additional parameters for immunity). There was no significant improvement ($P=0·17$) by having a different negative binomial constant k for each age group compared to a single negative binomial constant common to all age groups. This suggested that the negative binomial constant did not vary significantly with age. The most likely value (±95% confidence limits) of the parameters and the negative binomial constant is reported in Table 1. The most likely variation of parasite abundance with 95% confidence bands and the observed parasite abundance is illustrated in Fig. 2.

Farm dogs

In the case of the farm dogs there was a significantly improved fit with the full model (equation 4) containing the extra parameters in the model ($P<0·005$) compared to the nested model. The most likely (±95% confidence limits) value of the parameters in the model is reported in Table 2. The value of a indicates that there is some level of protective immunity to reinfection in the farm dog population. There was no significant improvement ($P=0·099$) by having a different negative binomial constant k for each age group compared to a single negative binomial constant common to all age groups. The value of the common negative binomial constant k and 95% confidence limits is reported in Table 2. The predicted variation of parasite abundance with age and 95% confidence bands is illustrated in Fig. 3. The actual observed parasite abundance is also illustrated in Fig. 3.

Bayesian inference

The posterior values of the parameters in the model, given the priors and the data, is illustrated in Table 1 (for the village dogs) and Table 2 (for the farm dogs). The posterior Bayesian median value and 95% confidence bands of the variation of parasite abundance with age is illustrated in Fig. 2 (for the village dogs) and Fig. 3 (for the farm dogs).

DISCUSSION

The results of the research described in this paper have a number of important implications. Firstly, it is the first comprehensive survey of the dog populations in southern Kazakhstan since the description of the new epidemic of hydatid disease in that area (Shaikenov *et al*. 1999*a*, *b*; Torgerson *et al*. 2002). Of the two types of dogs studied, the farm dogs appear to be the most heavily infected animals with both a high prevalence rate of 23% and high mean abundance of infection of 631 parasites per dog. The village dogs are infected but at lower levels. This is probably caused by the fact that farm dogs are more likely to be exposed to greater amounts of infected sheep offal as sheep in Kazakhstan are heavily infected with hydatid cysts (manuscript in preparation). Village dogs are more likely to be kept as pets and, although significant numbers of livestock are kept on small units in villages, there would appear to be much lower rates of transmission to village dogs. The data were obtained by purgation with arecoline. This method can underestimate the prevalence and abundance of *Echinococcus*, so the true

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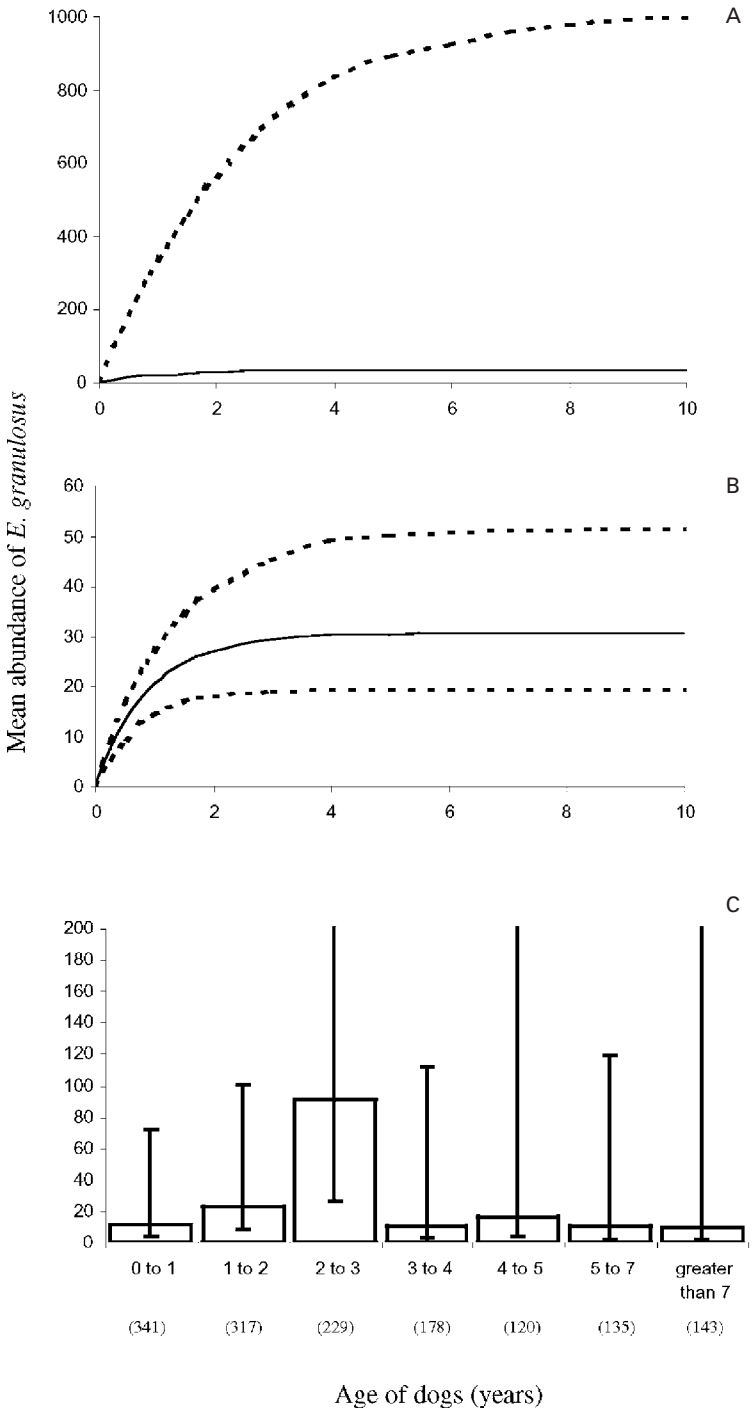

Fig. 2. Most likely variation of parasite abundance with age (—) and 95% confidence bands (- -) for the village dogs (A); posterior Bayesian variation of abundance with age (—) and 95% confidence bands (- -) (B). Mean observed abundance (±95% negative binomial confidence interval) (C). Sample sizes are indicated in parentheses.

abundance and prevalence may be higher than reported here. In the parameterization of the model, therefore, it is possible that the infection pressure in both groups of dogs (in terms of infectious parasites per year, i.e. h) could be higher. However, the only alternative technique that can give greater accuracy for parasite abundance is necropsy, which is not possible in working dogs or pets. Alternative diagnostic tests such as copro-antigen (e.g. Allen *et al.* 1992) are only qualitative and not quantitative and thus would be limiting for modelling transmission and estimating parasite biomass. The latter in particular is important for determining the risk of transmission to humans.

There have been few attempts at modelling parasite abundance data using the negative binomial distribution to describe the error variance. In a comparison of methods (Wilson, Grenfell & Shaw, 1996) it was demonstrated that by using classical linear modelling techniques there was a high probability

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Table 2. Maximum likelihood and Bayesian posterior values of the parameters and the negative binomial constant k in the model for farm dogs and their 95% confidence limits

Parameter	Most likely	Lower 95%	Upper 95%	Bayesian posterior median value	Lower 95%	Upper 95%
h	2967	1112	7871	3070	2659	3574
a	$3{\cdot}32\times10^{-4}$	$2{\cdot}71\times10^{-5}$	$1{\cdot}09\times10^{-3}$	$3{\cdot}03\times10^{-4}$	$2{\cdot}19\times10^{-4}$	$4{\cdot}62\times10^{-4}$
μ	1·01	0·25	4·93	1·09	0·73	1·47
γ	0·0197	0·0002	0·115	0·0193	0·0184	0·0197
k	0·02699	0·02252	0·03204	0·02698	0·02694	0·02699

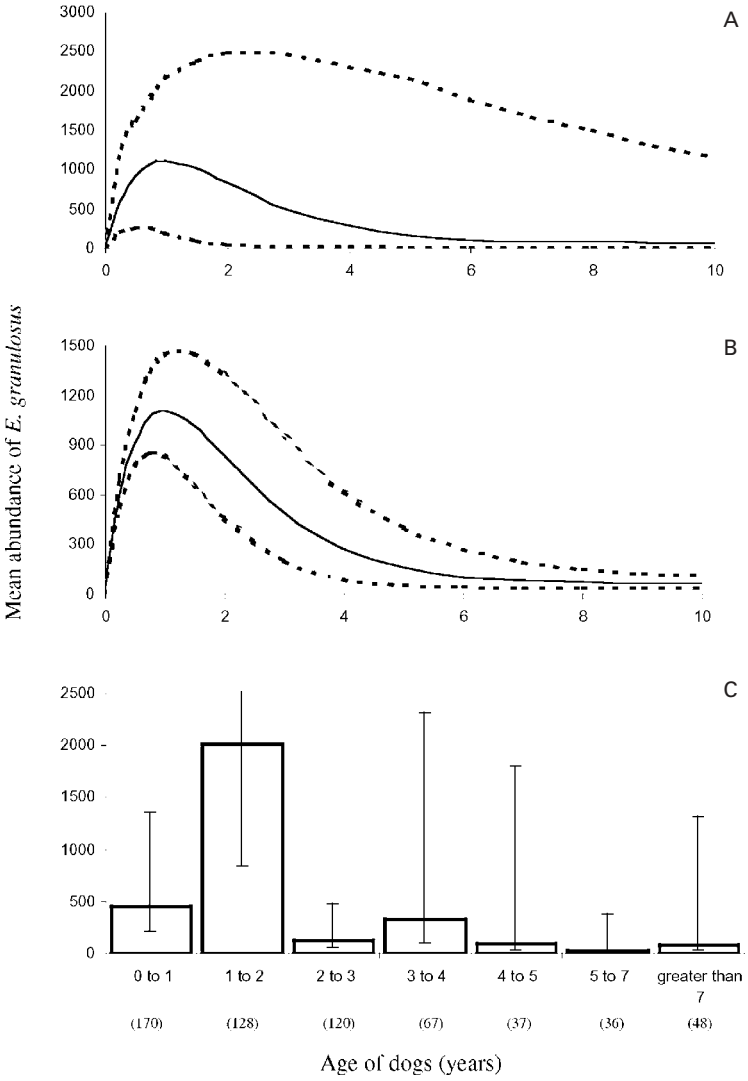

Fig. 3. Most likely variation of parasite abundance with age (—) and 95% confidence bands (- -) for the farm dogs (A); posterior Bayesian variation of abundance with age (—) and 95% confidence bands (- -) (B). Mean observed abundance (±95% negative binomial confidence interval) (C). Sample sizes are indicated in parentheses.

of errors, and even with general linear modelling techniques, there was sometimes failure to detect heterogeneities in the data. Pacala & Dobson (1988) also suggested that the patterns that emerge with non-linear maximum likelihood models could differ markedly from more conventional techniques, particularly when sample sizes are small. Using the non-linear maximum likelihood techniques described in this paper, with the negative binomial distribution to describe the error variance in the data, is the most mathematically robust analysis of the data. Such a robust mathematical approach to the modelling of *E. granulosus* is essential because of the extreme levels of aggregation of parasites within the host. The negative binomial constant in both groups of dogs was very small, thus infected dogs often had high burdens even when the prevalence rates were modest. The reason for this extreme distribution is

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due, partly at least, to the intense aggregation of the infectious stages. A hydatid cyst in the intermediate host can contain many thousands of protoscolices: thus a single infectious insult can result in the establishment of large numbers of adult tapeworms in the intestine. This extreme aggregation was the principal reason why the confidence intervals of the parameters were broad despite having a large sample size.

The Bayesian techniques did improve the certainty of the posterior probability distributions of the parameters in the model. This is illustrated by the tighter confidence intervals of the parameters and the narrower confidence bands of the model fit. However, using a Bayesian approach is only as good as the estimates of the prior distributions. It is possible that using the data without the prior distributions gives a better description of the parameters in the model. In this model the life-expectancy of the parasite is assumed to be independent of the parasite burden in the host. This is supported by the data as the maximum likelihood values of the life expectancy was similar for both village dogs with a low mean parasite burden and farm dogs with the substantially higher mean burdens. Indeed, this value from both sets of dogs is similar to the experimental value obtained by Aminjanov (1975). However, these experiments gave a much narrower range of the life-expectancy of the parasite than the model did, thus additional Bayesian analysis was useful. The less well defined life-expectancy suggested by the probability density of the parameters given the model and the data was partly due to the fact that, for example, a shorter parasite life-expectancy and higher infection pressure gave similar likelihoods compared to a longer parasite life-expectancy and lower infection pressure. These two scenarios were less likely than the maximum likelihood value but could fall within the confidence boundaries of the likelihood profile. Thus, by utilizing prior experimental data the parameters were better defined and this more precise definition could be beneficial for more accurate control simulation of echinococcosis.

The level of herd immunity suggested by the model is interesting. Firstly, it suggests that, under prevailing conditions of high infection pressure seen in the farm dog population, there is significant protection against re-infection. However, in the village dog population the best fit was the nested model with no acquired protective immunity. Although the summary data illustrated might suggest that there is a decrease in abundance in older village dogs, the confidence intervals suggest why this decrease was not significant. All the groups of older village dogs had an upper 95% confidence interval that was greater than the group of dogs aged 2–3 years, which was the group with the highest observed abundance. This contrasts markedly with the finding that only 1 group of older dogs had an upper 95% confidence limit that included the observed abundance of dogs aged 1 to 2 years, the group of farm dogs with the highest observed abundance. Thus it is only possible to fit a curve to the summary data for farm dogs, encompassing all the 95% confidence limits, that has a declining mean abundance in older animals and is consistent with equation (3) (with $a>0$). An attempt to fit any curve described by equation (4) will not include the confidence limits of some groups of farm dogs. However, either equation can be made to encompass all the confidence limits of the summary data for village dogs, therefore the equation with fewer parameters (equation 4) is the better fit. Consequently, these results are consistent with the idea that herd immunity is likely to be less under conditions of low infection pressure as suggested by Anderson & May (1985). These phenomena have been observed with some taeniid spp. in intermediate hosts (Gemmell, 1990; Torgerson *et al*. 1998) but not previously in their definitive hosts.

The analysis does assume that the parasite is in an equilibrium steady state in the definitive host population. Since the human incidence of disease has been increasing this could suggest that the parasite may not be in such a steady state. The increase in human incidence was first detectable in 1996 and there is evidence (unpublished) that the rate of increase of human incidence is now slowing. Changes in reported human incidence occur some years after any change in transmission between animals. The sheep population, though decreased substantially since the collapse of the Soviet Union (Torgerson *et al*. 2002) appears to have stabilized since 1997 which would have given an opportunity for a new steady state to establish. Finally, unpublished data also show that there is a linear increase in the mean abundance of hydatid cysts with age in sheep. If a new steady state had not yet established itself, the abundance in old sheep would be less than that observed. Nevertheless, it is possible that a new steady state is not yet in place and this would lead to greater uncertainty in the parameters of the model.

The model described in this paper assumes that there is constant infection pressure across all age classes of dogs. Because of this the most likely explanation of the decreased abundance in older farm dogs is due to the acquisition of acquired immunity in response to high infection pressure. Alternatively host behaviour could be changing, resulting in old dogs having a lower probability of exposure. This could be modelled by a change in infection pressure with age rather than the acquisition of immunity. However, the data itself mitigate against this possibility. If a decrease in infection pressure were responsible for the observed decrease in abundance in old farm dogs, the same phenomenon might be observed in the village dog population. This latter population gave a better fit to the nested model. Thus, the absence of a decline in abundance in

conditions of low infection pressure, but its presence in conditions of high infection pressure, is evidence that acquired host immunity is the most likely explanation of the observed age distribution in farm dogs. Furthermore, there is evidence of some degree of acquired immunity following experimental infection in dogs (Gemmell, Lawson & Roberts, 1986). In addition, no differences in susceptibility to infection of naïve dogs of ages 3 months, 6 months and over 2 years. Similarly, lower abundance rates of *E. multilocularis* have been observed in adult foxes compared to juvenile foxes (Hofer *et al*. 2000).

In conclusion this report, by using extensions of the models of Roberts *et al*. (1986, 1987), has suggested that herd immunity may be a density-dependent constraint in the transmission dynamics of *E. granulosus* under conditions of high infection pressure in dogs in Kazakhstan. This would increase the basic reproduction ratio of the parasite to a greater value than would be the case in the absence of immunity in either definitive or intermediate host and hence act as a stabilizing factor in the parasite population.

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