Distribution of *Ascaris suum* in experimentally and naturally infected pigs and comparison with *Ascaris lumbricoides* infections in humans

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(*Received 22 April 1998; revised 29 May 1998; accepted 29 May 1998*)

SUMMARY

This paper describes the distribution of *Ascaris suum* in experimentally and naturally infected pigs, and offers a comparison with *A. lumbricoides* infections in humans. In the first study, worms were recovered post-mortem from a group of 38 pigs that had been trickle inoculated with 10000 infective *A. suum* eggs twice weekly for 12 weeks. In the second study, worms were collected from a group of 49 pigs that had been kept on a pasture contaminated with infective *A. suum* eggs for 10 weeks, after which they received treatment with an anthelmintic; they then were turned out on the same pasture for a second 10-week period before slaughter. The worm burdens of the naturally infected pigs were recorded both at treatment and post-mortem. Mean worm counts were similar at all occasions but the prevalence of infection was higher in the trickle infected and naturally reinfected pigs. Furthermore, the prevalence in naturally infected pigs increased significantly over the study period. Worm burden distributions in all groups were heavily overdispersed, but the distribution patterns differed significantly between groups: lower exposure (initial natural infection) gave a low prevalence and an almost uniform distribution of worm burdens among infected hosts. Continued or higher exposure (trickle and natural re-infection) resulted in increased prevalence and a reduction in the proportion of hosts with increasing worm load. A positive correlation was found between initial and reinfection worm burdens in the naturally infected pig population, suggesting that individual pigs are predisposed to a high or low intensity of infection. The prevalence and intensity as well as the distribution observed for *A. suum* infection in pigs were comparable to those reported for *A. lumbricoides* in endemic areas, and there is evidence for predisposition to *A. suum* in pigs, with an estimated correlation coefficient similar to that found in humans. It is concluded that *A. suum* infections in pigs are a suitable model to study the population dynamics of *A. lumbricoides* in human populations.

Key words: *Ascaris suum*, pigs, exposure, negative binomial distribution, overdispersion, *Ascaris lumbricoides*.

INTRODUCTION

The distribution of helminth infections within their host population is typically aggregated or overdispersed, with the majority of worms being harboured by a minority of the population (Anderson & May, 1978; Anderson & Gordon, 1982; Shaw & Dobson, 1995). The importance of this distribution to parasite population dynamics has implications for density dependence, the relationship between morbidity and parasite burden, and its interaction with population genetics of both hosts and parasites (Anderson & Medley, 1985; Bundy & Medley, 1992; Anderson, Romero-Abal & Jaenike, 1995). If the effects of control strategies are to be predicted accurately, a mechanistic description of the causes of this parasite distribution is required (Medley, 1992, 1994).

A commonly applied empirical description of heterogeneous parasite distributions is the negative binomial probability distribution (Bliss & Fisher, 1953; Crofton, 1971*a*, *b*; Anderson & May, 1985), where an inverse measure of aggregation, the parameter k, together with the mean intensity of infection, specify the distribution of worms between hosts. The major factors thought to be responsible for overdispersion include spatial discontinuity in distribution of infective stages (as sampled by hosts), heterogeneity in host behaviour, differences in innate susceptibility and other genetically determined factors (Wakelin, 1984). However, there has been little systematic investigation of the relative importance of these effects (Bundy & Medley, 1992), chiefly because of the close interdependence and interaction between them. For example, differences between

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https://doi.org/10.1017/S0031182098003382 Published online by Cambridge University Press

hosts in innate susceptibilities or immunological competencies can only be detected when exposure is controlled.

Infections with the large roundworm *Ascaris suum* in pigs can be used as a model for *A. lumbricoides* infections in humans for several reasons. Firstly, *A. lumbricoides* and *A. suum* are very closely related ascarid species (Anderson, 1995). Secondly, both *A. lumbricoides* in man and *A. suum* in pigs constitute natural host–parasite relationships, with migratory cycles that are thought to be similar since there are no existing data that unequivocally demonstrate the contrary (Murrell *et al.* 1997). Thirdly, the pig has been extensively used as a model in biochemical research because of the anatomical, physiological, immunological, metabolic and nutritional similarities between humans and pigs (Swindle, 1992). For instance, *A. suum* infections in growing pigs were found to be a suitable model for *A. lumbricoides* infection in children (Stephenson *et al.* 1980; Forsum, Nesheim & Crompton, 1981). Correspondingly, Willingham & Hurst (1996), on the basis of successful studies on *Schistosoma japonicum* infections, advocated the use of the pig as a model for human schistosomosis.

While it is well documented that infections with *A. lumbricoides* in humans are characteristically overdispersed (e.g. Anderson & May, 1985; Elkins, Haswell-Elkins & Anderson, 1986; Bundy *et al.* 1987; Guyatt *et al.* 1990), relatively little research has been done into the nature of *A. suum* distributions within pig populations or the mechanisms that generate them. Experimental inoculations with single or multiple doses of *A. suum* eggs have resulted in overdispersed worm counts in pigs (Jørgensen *et al.* 1975; Urban, Alizadeh & Romanowski, 1988; Eriksen *et al.* 1992*b*; Roepstorff *et al.* 1997) while information about natural *A. suum* infections in pig production herds is based either on prevalence studies using faecal egg counts (Roepstorff & Jorsal, 1989; Roepstorff & Nansen, 1994; Roepstorff, 1997) or on slaughterhouse surveys (Bindseil, 1974; Jacobs & Dunn, 1969; Bøgh *et al.* 1994). However, the distribution of *A. suum* worm counts after continuous exposure to infective eggs either by experimental or natural infection has rarely been studied in detail. Eriksen *et al.* (1992*b*) trickle-infected pigs with low doses of *A. suum* eggs for 10–16 weeks and found that 10% of the pigs harboured 80% of the worms at slaughter. Trickle infection of pigs with higher doses of *A. suum* eggs, i.e. stronger antigenic stimulation of the host, has not been reported previously but may provide additional information about the role of the immune response and possible dose dependencies. Evidence from single-dose experimental *A. suum* infections in pigs has shown that aggregation occurs regardless of dose level, and the resulting worm counts depended partly on dose given (Roepstorff *et al.* 1997).

One of the principal empirical observations concerning the generation of *A. lumbricoides* distributions in human populations is predisposition, i.e. relatively heavily (lightly) infected individuals tend to re-acquire relatively heavy (light) worm burdens following anthelmintic treatment. This has been demonstrated for individuals and families using data from field studies (Croll & Ghadirian, 1981; Elkins *et al.* 1986; Holland *et al.* 1989; Chan, Kan & Bundy, 1992; Forrester *et al.* 1990). This correlation is not conclusive, and rank correlation coefficients are typically less than 0·5 (Keymer & Pagel, 1990). In pigs, however, susceptibility to reinfection has to our knowledge only been tested through abbreviation of early *A. suum* infections with anthelmintic drugs, followed by a single dose challenge infection (e.g. Stewart *et al.* 1985; Stankiewicz, Jonas & Froe, 1992). This is unlikely to be an accurate reflection of the population dynamics of *A. suum* infection under practical conditions which include anthelmintic treatment of pigs. The infection-treatment-reinfection design used in the present study will provide information both about the population dynamics of *A. suum* and predisposition in pigs in a continuously exposed population.

In this paper we use experimental data to address the pattern of dispersion of *A. suum* between hosts. This parasite is significant both as an important parasite in pig production and as a model for the human roundworm, *A. lumbricoides*. We compare both the form of the overdispersed distribution by reviewing published data, and consider the exposure dependence of the parasite distribution using novel experimental results. The aims of the present study were (1) to measure and investigate the prevalence and distribution of *A. suum* worms within trickle and naturally infected pig populations; (2) to study reinfection with *A. suum* in naturally infected pigs after anthelmintic treatment; (3) to investigate predisposition in pigs to *A. suum* infection; (4) to compare aspects of the population dynamics of *A. suum* and *A. lumbricoides*.

MATERIALS AND METHODS

Trickle-inoculated pigs

Thirty-eight helminth-naive Danish Landrace × Yorkshire × Duroc cross-bred male pigs, obtained from a specific pathogen-free (SPF) herd and weighing 25–30 kg, were kept on a helminth-free pasture from December 1995 to March 1996. The pigs were trickle inoculated through the feed (group feeding) twice weekly with 10000 infective *A. suum* eggs/pig for a period of 12 weeks. Faecal samples were taken from each pig bi-weekly starting at turnout and analysed for *A. suum*, eggs using a concentration McMaster method with a lower detection limit of 20 eggs per gram faeces (epg) (Roepstorff & Nansen, 1998). Twelve weeks after

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Table 1. Parasitological and pathological findings together with prevalence, distribution and degree of aggregation of *Ascaris suum* in trickle inoculated and naturally infected pigs

Experiment	Number of pigs	Mean worm count	Mean length ♂ worms in cm (S.D.)	Mean length ♀ worms in cm (S.D.)	Mean no. liver white spots	Liver fibrosis	Prevalence of infection (%)	$s^2/\bar{x}$ variance to mean ratio	k neg. binomial (95% CI)
Trickle inoculation*	40	3·8	N.A.	N.A.	19	N.A.	25	26·6	0·07 (0·04–0·12)
Trickle inoculation	38	10·6	13·1 (1·78)	18·6 (3·26)	55	+ + +	63	43·1	0·26 (0·17–0·40)
Natural infection	49	10·4	12·1 (2·33)	18·1 (4·62)	N.A.	N.A.	40	68·4	0·09 (0·05–0·13)
Natural reinfection	49	9·3	14·3 (2·86)	20·4 (4·71)	5	+ +	84	13·1	0·69 (0·44–1·10)

* Calculated from Eriksen *et al.* (1992*b*): the pigs were trickle inoculated with 25 or 500 *A. suum* eggs twice weekly for 10–16 weeks.
N.A., Not available.

turnout, all pigs were slaughtered and the contents of the small intestine sieved to recover macroscopically detectable (> 2 cm) worms. All worms were counted, sexed and measured and subsequently stored in 70% ethanol. The number of liver white spots and the degree of liver fibrosis, scored as slight (+), moderate (++) or severe (+++), were recorded for each pig at slaughter.

Naturally infected pigs

Fifty helminth-naive Danish Landrace × Yorkshire × Duroc cross-bred male pigs, obtained from the above-mentioned SPF herd and weighing 25–30 kg, were introduced in early May 1996 to a pasture that had been contaminated with *A. suum* eggs by infected pigs in the 2 preceding years. All pigs received a nose-ring at the start of the experiment to prevent complete destruction of the grass sward. The pigs were allowed to graze the pasture for 10–11 weeks, after which they were all housed in individual cages that prevented coprophagia. The pigs were then treated by stomach intubation with piperazine dihydrochloride (200 mg/kg body weight), which has shown an efficacy of > 99% against *A. suum* (Steffan *et al.* 1988). Adult and macroscopically distinguishable (> 2 cm) immature *A. suum* worms in the faeces of individual pigs were collected manually twice daily within 3 days following deworming, counted, sexed and measured. Subsequently all pigs were reintroduced to the infected pasture. Faecal samples were taken biweekly starting at turnout and analysed as described above. Ten weeks post-treatment, i.e. 20 weeks after turnout, all pigs were slaughtered. The necropsy procedures were as described for the trickle inoculations. One pig had to be culled because of a fractured leg 12 weeks post-turnout and was omitted from the data analysis.

Statistical analysis

Individual worm burdens, recovered from the faeces of naturally infected pigs following anthelmintic treatment and post-mortem from the small intestine of experimentally and naturally infected pigs, were analysed using the SAS software package, version 6.12. The worm count distributions of both experimentally and naturally infected pigs were compared using the Kolmogorov–Smirnov test or the Wilcoxon Signed-Rank test (paired data). A Spearman rank correlation coefficient and Kendall's τ were calculated for the association between pre- and post-treatment worm burdens. Pre- and post-treatment prevalences in the naturally infected pigs were compared using McNemar's test. The degree of overdispersion of worm counts in experimentally and naturally infected pigs was characterized by variance to mean ratios (hereafter referred to as $s^2/\bar{x}$) and the maximum likelihood estimates of k, the

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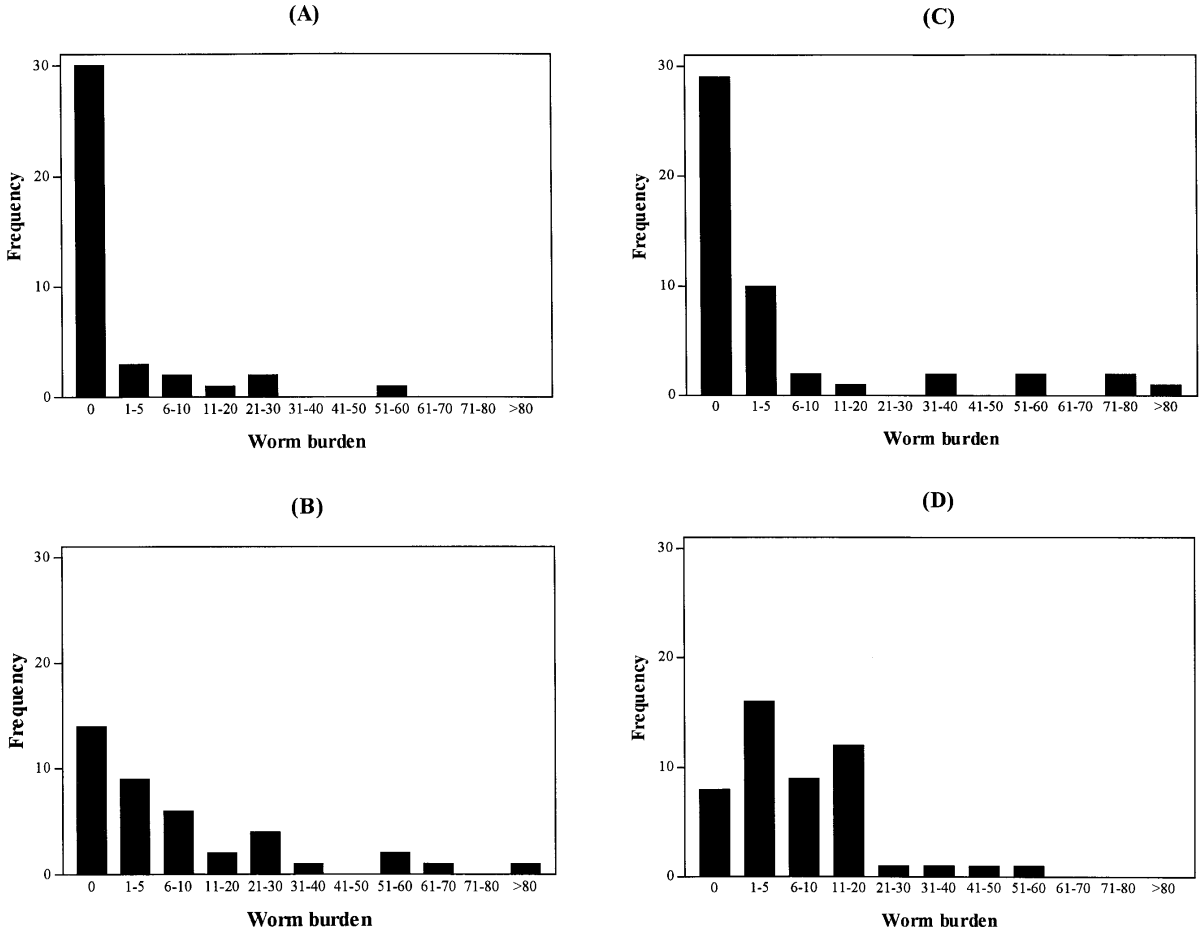

Fig. 1. *Ascaris suum* distributions in pigs. (A) Trickle infection of 40 pigs with 25 or 500 *A. suum* eggs twice weekly for 10–16 weeks (redrawn from Eriksen *et al.* 1992*b*). (B) Trickle infection of 38 pigs with 10000 *A. suum* eggs twice weekly for 12 weeks. (C) Natural infection of 49 pigs during 10 weeks on pasture contaminated with *A. suum* eggs. (D) Reinfection distribution of 49 pigs on the same contaminated pasture 10 weeks after anthelmintic treatment.

parameter of the negative binomial distribution, which were calculated using the method of Bliss & Fisher (1953).

RESULTS

The parasitological and pathological findings for both experiments are shown in Table 1. The mean worm burden in trickle inoculated pigs (10·6) was similar to the mean worm counts in naturally infected pigs, both at time of treatment (10·4) and at slaughter (9·3). However, in the naturally infected pigs the prevalence of infection increased significantly from 40 % at the time of anthelmintic treatment to 84 % at the time of necropsy ($P < 0{\cdot}05$). The livers of the trickle-infected pigs all showed moderate to severe diffuse fibrosis and numerous white spots (range: 10 to > 100) were counted on the livers of 25 out of 38 pigs. On the livers of the naturally infected pigs low numbers of white spots (range: 1 to 35) were found in 41 out of 49 pigs and slight to moderate liver fibrosis was seen in all but 6 pigs.

Worm burdens recovered from trickle infected and naturally infected pigs were heavily over-dispersed, with $s^2/\bar{x} \gg 1$ and $k < 1$ in all 3 cases (Table 1). A total of 21 % of the trickle-infected pigs harboured 80 % of the worms recovered at slaughter. Of the naturally infected pigs 10 % harboured 80 % of the worms expelled at treatment, compared to 39 % of the pigs harbouring 80 % of the worms recovered at slaughter. For comparison, the results from the low-dose trickle infections reported by Eriksen *et al.* (1992*b*) are reproduced in Table 1. These authors trickle inoculated pigs with either 25 or 500 *A. suum* eggs twice weekly and conducted serial slaughterings from week 10 to week 16 post-infection. Analysis of their data revealed a strong overdispersion ($s^2/\bar{x} = 26{\cdot}6$, $k = 0{\cdot}07$) with 10 % of the pigs harbouring 80 % of the worms, but the mean worm burden was lower (3·8).

The worm burden distributions of the trickle inoculated and naturally infected pigs are shown in Fig. 1A–D. All 4 distribution curves are positively skewed, indicative of parasite aggregation. Statistical comparison of the worm burden distributions using the Kolmogorov–Smirnov (K–S) test revealed that the distribution of worms in the low-dose trickle infection and the worm counts at treatment in naturally infected pigs were similar ($P = 0{\cdot}64$) (Fig. 1A and C); this was also found for the worm

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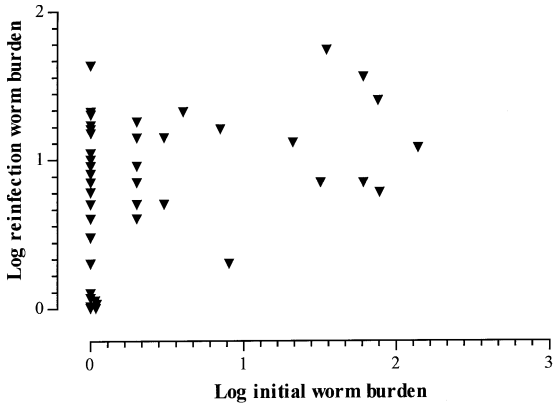

Fig. 2. Evidence for predisposition to *Ascaris suum* infection in naturally infected pigs. The data indicate, for individual pigs, the initial worm burdens versus the worm burdens acquired after anthelmintic treatment and a period of reinfection. There is a significant correlation between initial and reinfection worm burdens in individual pigs.

Table 2. *Ascaris suum* burdens after reinfection in naturally infected pigs 20 weeks post-turnout, classified by initial worm burden recovered at anthelmintic treatment (10 weeks post-turnout)

Intensity category	*N*	Worm burden at treatment		Worm burden after reinfection	
		Mean	Range	Mean	Range
No worms	29	0	0	6·8	0–20
Low burden (< 10)*	12	2·3	1–7	7·7	1–20
High burden (> 10)	8	61·9	20–138	19·1	5–54

* A mean burden of 10 worms was recovered at anthelmintic treatment.

distributions resulting from the high-dose trickle infection and the natural reinfection study ($P = 0{\cdot}11$) (Fig. 1B and D). However, a significant difference was found between the worm count distributions in both trickle-infected groups of pigs using the K–S test ($P < 0{\cdot}01$) (Fig. 1A and B). Furthermore, the distribution of worm burdens in naturally infected pigs changed significantly after the reinfection period ($P < 0{\cdot}001$, Wilcoxon Signed-Rank test) (Fig. 1C and D).

The size of the worm burden reacquired after anthelmintic treatment in naturally infected pigs was positively associated with the intensity of infection before treatment (Fig. 2). There was a significant correlation between initial and reinfection worm burdens in the naturally infected pig population (Spearman rank correlation coefficient $r_s = 0{\cdot}39$, $n = 49$, $P < 0{\cdot}01$), suggesting that individual pigs are predisposed to a high or low intensity of infection. Much of the positive correlation is due to the 8 pigs

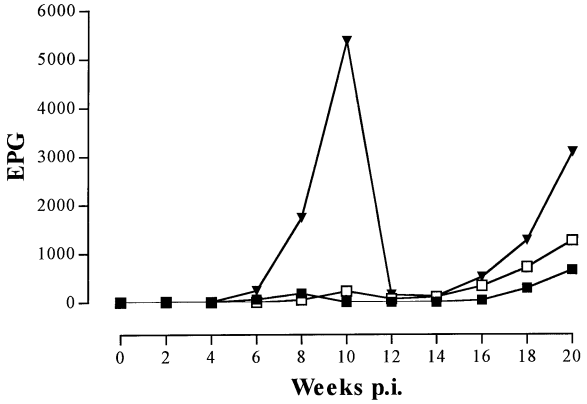

Fig. 3. Relationship between initial infection intensity and rate of reacquisition of *Ascaris suum* infection in pigs as measured by egg counts. The intensity classes are the same as those shown in Table 3: (■) no worms ($n = 29$), (□) low burden ($\leqslant 10$ worms, $n = 12$) and (▼) high burden (> 10 worms, $n = 8$), all determined at time of anthelmintic treatment. The infection intensity is expressed as mean number of eggs per gram faeces (epg). The pigs were treated with anthelmintic 10 weeks p.i.

that harboured no worms at both occasions. After correction for tied values the correlation was slightly lower but still statistically significant (Kendall's $\tau = 0{\cdot}31$, $n = 49$, $P < 0{\cdot}01$).

Based on the worm burdens recovered by anthelmintic treatment the naturally infected pigs were divided into 3 classes: (i) no worms, (ii) low burden (worm counts $\leqslant 10$, which was the mean worm burden recovered) and (iii) high burden (worm counts > 10). The mean worm burdens pre- and post-treatment after classification are shown in Table 2. They illustrate that pigs with high worm burdens on initial infection have a reduced worm load on reinfection but remain higher, whereas the groups with lower initial worm burdens tend to merge on reinfection. This is further illustrated by the relationship between intensity of infection as measured by egg counts and the re-acquisition of *A. suum* worms shown in Fig. 3. Again, individuals excreting high numbers of eggs at treatment show higher egg counts after reinfection, although the rate of increase is slower than during the initial infection period. In contrast, the 2 lower groups have higher egg counts at slaughter than at treatment.

DISCUSSION

The major aim of the present study was to investigate the distribution of *A. suum* in experimentally and naturally infected pig populations. The results of this study clearly show that *A. suum* worm burden distributions in both experimentally and naturally infected pigs are highly overdispersed. The data further suggest that some aspects of *A. suum* population dynamics are very similar to those of *A. lumbricoides*.

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The prevalence of *A. suum* infection varied from 40 to 84% in the present study. Trickle inoculation with high doses of eggs resulted in a higher prevalence of infection compared with the low-dose trickle infections reported by Eriksen *et al.* (1992*b*). The higher prevalence in both trickle-inoculated pigs and the naturally reinfected pigs may reflect differences in exposure. In the naturally infected pigs the prevalence of infection increased significantly after anthelmintic treatment, while the intensity of infection remained at approximately 10 worms/pig. This increase in prevalence is somewhat surprising since age resistance to *A. suum* has been shown to occur (Eriksen *et al.* 1992*a*) and increased resistance with exposure might have been expected.

However, other factors may have interfered with the transmission of infection and the build-up of immunity. Firstly, the summer of 1996 was quite warm and dry, which caused the soil on the experimental pasture to become harder than usual. Combined with the application of nose-rings, this hindered the rooting behaviour of the pigs, thus limiting initial uptake of infective eggs, while rainfall during the reinfection period may have improved rooting possibilities. Secondly, at the same time the weather conditions in the summer of 1996 were favourable for the embryonation of the large amount of overwintered, non-infective eggs that were found in the soil on the same pasture. When the pasture infectivity was tested before (spring 1996) and after (autumn 1996) the present study was conducted, using tracer pigs and soil egg counts, it was found to be sufficient on both occasions (Roepstorff, unpublished observations). Note that the high dose trickle-infected pigs were kept on a clean pasture and could not have reinfected themselves as *A. suum* eggs do not embryonate under winter conditions (Larsen, 1996).

The distributions of the individual worm counts consistently showed an overdispersed pattern in the current experiments and a similar distribution was observed in the study of Eriksen *et al.* (1992*b*), indicating that the distribution of *A. suum* in pig populations is aggregated regardless of the nature, duration, frequency or dose level of the exposure. This has also been shown in single dose *A. suum* infections (Roepstorff *et al.* 1997).

Although overdispersed, significant differences were found between the worm burden distributions. This is reflected in the value of k, which is very low for the low-dose trickle infection and the naturally infected pigs at treatment, but increases with higher exposure (high-dose trickle and natural reinfection), indicating reduced aggregation. Figure 1 clearly shows that differences in exposure resulted in 2 distinct overdispersed distributions: those with lower exposure have a high proportion of uninfected hosts and an almost uniform distribution among the infected hosts, whereas those with a higher exposure show a lower number of uninfected hosts and a gradual reduction in the proportion of hosts with increasing worm load. The data suggest that this difference is caused mainly by uninfected hosts acquiring relatively low worm burdens with increased exposure, resulting in a higher prevalence of infection.

An interesting insight into the mechanisms that generate overdispersion is that individual animals under natural exposure appear to maintain a relatively constant position when ranked by worm burden. The same is true for egg counts when animals are grouped based on pre-treatment worm load. Although predisposition has been shown for *Heligmosomoides polygyrus* and *Aspiculuris tetraptera* infections in mice (Scott, 1988), it has not been demonstrated previously in pigs infected with *A. suum* or any other animal species to the best of our knowledge.

One of the aims of this study was to compare aspects of the population dynamics of *A. suum* and *A. lumbricoides*. The prevalence and intensity of *A. suum* infection in animals under high exposure found in the current study are comparable to those reported for *A. lumbricoides* in highly endemic areas (Anderson & May, 1985). More interestingly, the worm distributions and estimated values of k in these groups are also very similar (Guyatt *et al.* 1990). The values of k in the less exposed animals (higher degree of overdispersion) are lower than those reported for *A. lumbricoides*. However, it should be borne in mind that the animals used in these studies were parasite naive at the start of the experiments, unlike humans in endemic areas. In the case of *A. lumbricoides* this would correspond with k values increasing through early childhood, for which there is some evidence (Bundy, Kan & Rose, 1988).

The pig model allows quantitation of worm burdens by means of both expulsion studies and post-mortem examination. The anthelmintic treatment of naturally infected pigs in the current study corresponds with the treatment + reinfection protocol frequently reported for *A. lumbricoides* studies in humans, although the reinfection period in human studies is usually longer (see Keymer & Pagel, 1990), yet the patterns observed show a remarkable similarity. There is clear evidence for predisposition to *A. suum* in pigs, with an estimated correlation coefficient of similar magnitude to that found in humans. Also, the correlation between initial and reinfection worm burdens is of the same form, apart from the fact that no pig that initially harboured worms was worm free at slaughter.

In conclusion, there is considerable scope for further study of *A. suum* population dynamics. Clearly, the distribution of parasites between hosts depends on a number of host and environmental factors, each of which could be studied in more

detail. Furthermore, it is not well understood how, or even if, this overdispersion affects production under different management systems, or how it should influence the design of control strategies. On the basis of the comparison presented here, we conclude that *A. suum* infections in pigs are a good model for the population dynamics and epidemiology of human ascariosis. The animal model offers the advantage of being able to conduct further experimentation in order to understand the underlying biological mechanisms, e.g. controlling exposure and/or diet. To this end, we are currently further studying the serology, pathology and parasite size data derived from these experiments.

The authors gratefully acknowledge the skilful technical assistance of Niels Midtgaard, Morten Cleeman Hors, Saulius Petkevičius and Audrius Furmonavičius. Liz Barnes is thanked for useful discussions of a previous draft. This study was supported by the Danish Research Foundation.

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