

Detecting interactions between parasites in cross-sectional studies of wild rodent populations¹

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ABSTRACT. There is extensive and convincing evidence from experimental studies that interactions exist between helminths of different species during concurrent infections in laboratory rodents. Among the strongest interactions are those that arise from immune responses of the hosts. However, detecting comparable relationships in data acquired from wild rodent populations has not been easy. In general, helminth infections in naturally occurring rodent populations show highly predictable trends; seasonal, host age-dependent and spatial variation in the abundance of core species and in helminth species richness are regularly reported aspects of these host-parasite communities. Controlling for these strong effects is therefore extremely important, if interactions between species are to be detected. One such interaction, the positive relationship between *Heligmosomoides polygyrus* and species richness of other helminths in European wood mice, *Apodemus sylvaticus*, has been found in four totally independent data-sets, three drawn from the U. K. and one from Portugal. These analyses provide strong evidence that at the level of species richness a highly predictable element of co-infections in wood mice has now been defined.

Key words: rodents, bank voles, wood mice, helminths, nematodes, interactions, associations, co-infections, immunity

Introduction

Like all living organisms parasites interact with the external environment and are subject to its influences through climatic factors that affect the development and survival of free-living transmission stages [1–3]. Likewise, they encounter and interact with other living organisms, including the host within which they live. However, hosts are not uniform and host factors (intrinsic factors such as age, sex, diet, genetic status, social position, life history strategy) play important roles in regulating susceptibility to infection [4–6]. Within hosts, parasites interact with members of their own species and with other parasites exploiting the same host, and it is the latter, the extent to which a given parasite species influences the abundance of other species parasitizing the same host, that forms the central issue in parasite community ecology. Interactions between species are the hall mark of community ecology,

and a defining feature of animal communities, distinguishing them from loose assemblages of animals that show no interactions, existing only because of a range of co-incidental external factors that result in their co-occurrence in a given location or host [7,8].

Theoretically, and based on experimental studies, interactions between species comprise a spectrum from the baseline of simple co-occurrence of species in the same host, through to potent interactions in which one species influences the environment within the host in a manner that benefits or impairs the survival of other species. In this paper, I hope to show that patterns of co-occurrence, that are compatible with positive, or synergistic, interactions between species can be detected in cross-sectional field data, but that their detection requires a detailed knowledge of the structure, stability and composition of helminth communities, and that this knowledge has to be factored into relevant analytical procedures.

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Co-occurrence of helminths in hosts

The co-occurrence of parasites is well known in the medical literature where it has often been referred to as polyparasitism [9–11]. Likewise, many papers exist in the veterinary [12] and zoological literatures indicating that it is the normal state in nature for a host to carry more than just one species of parasite at any point in time [9,13–21].

Data exist to show that some of these co-occurring species are more often encountered together than by chance and that heavy infections with one species predispose to heavy infections with the other. One example among human parasites is the well documented co-occurrence of *Ascaris lumbricoides* with *Trichuris trichiura* [22–24]. To give just one example, a highly significant positive relationship between the abundance of these two species was reported by Tchuem Tchuente et al. [25]. This relationship remained significant, although it was weaker indicating some degree of correlated exposure, when the authors controlled for differences between the five schools and twelve age classes of the children in the survey. These two species are known to have well-protected, tough eggs, and they are both transmitted by the faecal oral route. Therefore, children who practiced poor standards of hygiene are likely to have been more frequently exposed than those with higher standards of cleanliness to both species. In this case the co-abundance of *A. lumbricoides* and *T. trichiura* is not so much a reflection of interactions between these species, but rather of their common transmission strategies. There was no quantitative assessment of the degree of correlated exposure in this study but if appropriate data had been collected and if this additional control had been factored into the analysis, it is highly likely that the quantitative relationship between the intensity of infection with *A. lumbricoides* and *T. trichiura* will have largely disappeared.

Evidence for interactions from laboratory studies

The literature contains a large range of laboratory experiments in which interactions between helminths in rodent host systems have been investigated at a variety of different levels [26,27]. Among the pioneers of this approach, widely regarded as the father of the field of quantitative helminth community ecology [28,29] was John Holmes [30–32] working with *Hymenolepis diminuta* and *Moniliformis moniliformis*, two helminths that occupy the anterior region of the gut of rats. His conclusion that *M. moniliformis* holds its own, while *H. diminuta* retreats to the non-optimal distal regions of the small intestine, was one of the classic findings in this field. Holmes went on to provide an evolutionary framework for these types of interactions [33]. Another early contributor was Gerry Schad [34] working on the pinworms of Greek tortoises. His seminal work in this field established the concept of niche segregation and specialisation among closely related helminths sharing overlapping gut locations. This hypothesis has been debated and tested widely ever since and some have argued that in hosts such as fish there are many vacant niches and that the evolutionary pressure for niche segregation stems from the need to reinforce reproductive barriers and maximum utilisation of food resources [28,29,35,36].

Many parasites, including helminths, stimulate potent immune responses in their hosts, and interactions between species have been shown to arise in some cases through the host response, rather than stemming from direct interactions between the species concerned. Broadly speaking, five categories of such interactions have been described. Three of these generate negative interactions, where the presence of one species is detrimental to others. These are interactive expulsion where the non-specific effector elements of an immune response stimulated by one species have detrimental consequence for ano-

Table 1. Examples of synergistic interactions between intestinal helminths. In these examples the first species is *Heligmosomoides bakeri*, a species that depresses the immune response to other co-infecting species, prolonging survival of the latter (modified from the original in [43]).

Inducing parasite	Affected parasite	Reference
<i>H. bakeri</i>	<i>Rodentolepis microstoma</i>	[44]
<i>H. bakeri</i>	<i>Nippostrongylus brasiliensis</i>	[45,46]
<i>H. bakeri</i>	<i>Trichuris muris</i>	[47,48]
<i>H. bakeri</i>	<i>Trichinella spiralis</i>	[49,50]
<i>H. bakeri</i>	<i>Hymenolepis diminuta</i>	[51]
<i>H. bakeri</i>	<i>Hymenolepis citelli</i>	[52]

ther species that is present in the gut at the same [37–40]. Another is cross immunity between species [41] and the third is up-regulation of the host's capacity to mount Th2 responses by reinforcement of the Th2 pathway.

Alternatively, interactions can be positive or synergistic, with one species enhancing the survival of a second. Thus, the presence of some species of parasites can benefit other co-residing species through the host's weakened immune defences, these arising from a depressed immune capacity induced by the first species as part of its survival strategy, and a classic example of this is *Heligmosomoides bakeri*. When mice are infected with *H. bakeri* they sustain longer and heavier infections with a wide range of other species that have been administered concurrently (Table 1). It is also possible that by initiating the Th2 pathway helminths may increase the susceptibility of hosts to species that are better controlled by Th1 responses [42], although in practice most helminths succumb to Th2 rather than Th1 mediated host responses.

Deriving evidence of interactions from field data

Collectively the laboratory studies on *H. bakeri* provide strong evidence that this species is immunodepressive. We might expect, therefore, that *H. bakeri* and its close relatives in wild rodent populations should predispose the host to infection with other helminths. My colleagues, collaborators and I have looked specifically for data to test this idea, namely that in European wood mice the close relative of *H. bakeri*, *Heligmosomoides polygyrus* enhances the susceptibility of wood mice to infection with other species of helminths.

The usual approach to such studies is to cull rodents from appropriate study sites in batches, generating cross-sectional data at a point in time or over a set period. Analysis is usually then by tests based on correlations. The main problem with this approach, however, is that correlational tests can never unravel cause and effect, because significant correlations can arise from indirect relationships. Such tests on raw data can give spurious results because worm burdens of both candidate species may be aggregated in particular subsets of animals, giving an impression of correlation which is actually misleading.

In general, helminth infections in naturally occurring rodent populations show highly predictable

trends; seasonal, host age-dependent and spatial variation in the abundance of core species and in helminth species richness are regularly reported aspects of these host-parasite communities [53–57] and these can be measured and factored into analyses.

Therefore, with these provisos in mind and hypothesising that interactive relationships exist, we can make relevant predictions about the nature of relationships between co-infecting helminths, and taking into account quantified factors that may be responsible for aggregating parasites in some data subsets, test for their significance. If the same relationships can be demonstrated in different groups of animals sampled from ecologically contrasting sites in different climatic zones, it would be difficult to dismiss this as mere coincidence.

An obvious prediction to make then, based on the laboratory studies, might be that rodents carrying heavy populations with heligmosomatids should be more likely infected with other species, than animals that are not infected with heligmosomatids and we might expect also some quantitative positive relationship in abundance. To test these predictions, with colleagues and collaborators, I have explored three wood mouse datasets from the UK and one dataset from Portugal [58] in each of which *H. polygyrus*, was a dominant species, and in each of which a range of possible confounding factors was measured and recorded. Our results were reported in Behnke et al. [59,60] and I summarise some of the key findings here.

Studies on wood mice in southern England

Analysis of the data from our three site study in SE England [4,5] revealed that indeed some relationships were significant and robust. Firstly, the prevalence of the cestode *Catenotaenia pusilla* was higher among mice that also harboured *H. polygyrus*. This was tested in a model that included other factors known to affect the prevalence of both species including season, age and sex, and therefore controlled for the possible confounding effects of these factors. Nevertheless, the finding was significant; the co-occurrence of these two species (*C. pusilla* and *H. polygyrus*) was not confounded by other factors and was evident in all three study sites (Fig. 1).

We analysed raw abundance data also, confining the analysis only to those animals that harboured both species, and the initial analysis showed borderline significance (Fig. 2A; $r_s=0.24$, $n=68$, $P=0.054$). However, next we controlled for all possible confounding factors that had been quantified and that mi-

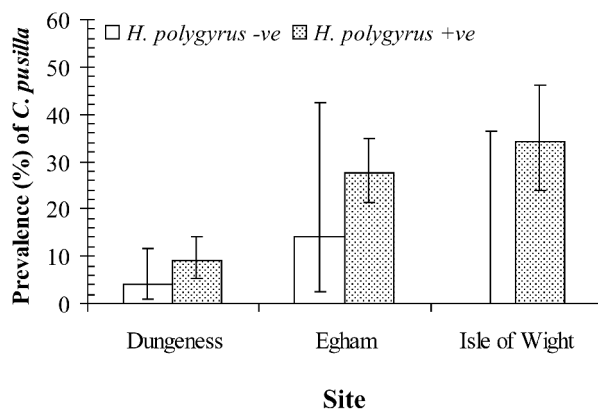


Fig. 1. The presence of *H. polygyrus* in wood mice increases the likelihood of infection with *Catenotaenia pusilla*, in each of three sites that were studied in SE England. The full details of the methodology and approach used for statistical analysis are given in [59]. The error bars are 95% confidence limits. Figure modified from [59].

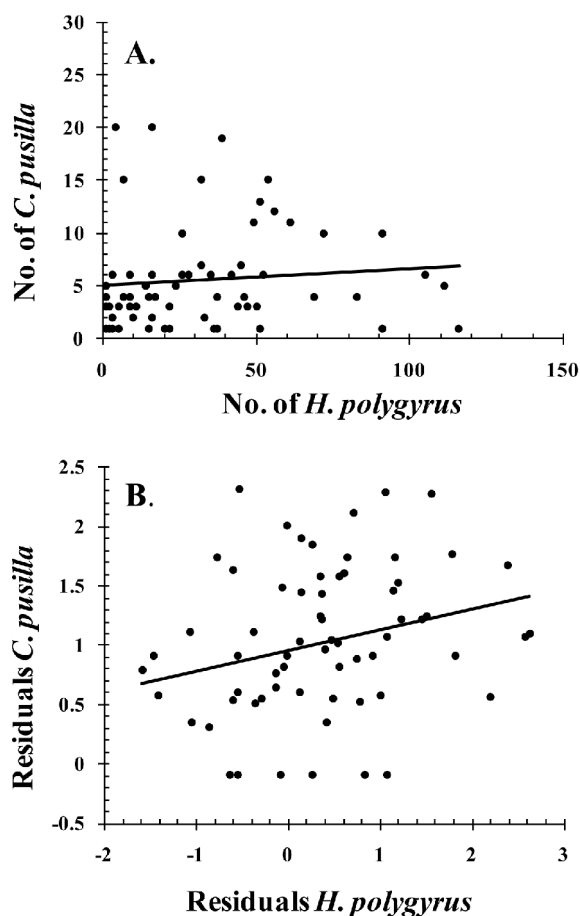


Fig. 2. Correlation between the intensity of infection with *H. polygyrus* and *C. pusilla* in the raw data-set (a) and in data adjusted for the role of other confounding factors (b). In b, the axes show the residuals of GLMs in which other factors have been taken into account. For full explanation see the text and [59]. Figure modified from [59].

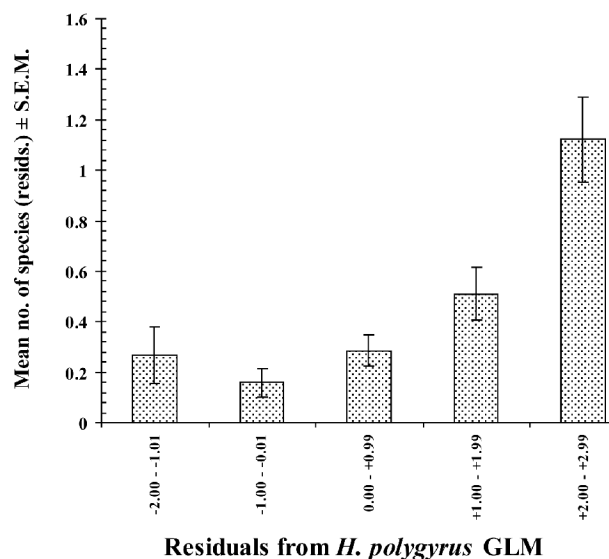


Fig. 3. Wood mice that carry more *H. polygyrus* for their subset, also have a higher species richness of other helminths for their subset ($r_s=0.45$, $n=179$, $P<0.001$). See text and [59] for further details including full statistical approach of these data. Figure modified from [59].

ght have contributed to the aggregation of both species in some subsets of mice. This was done by fitting the residuals of minimum sufficient GLM models, and the consequence was that the correlation improved quite markedly (Fig. 2B; $r_s=0.32$, $n=68$, $P=0.008$; [59]).

Another finding from these analyses was that wood mice that carried more *H. polygyrus* for their particular subset, also carried more other species of helminths. This is illustrated in Fig. 3 which shows the highly significant positive relationship that emerged after all other quantified factors, that may have generated correlated exposure, were controlled for. The figure shows the correlation between the residuals of minimum sufficient GLM models of both abundance of *H. polygyrus* and species richness confined to mice that were infected with *H. polygyrus* and at least one other species of helminth.

Studies on wood mice in Portugal

After completion and publication of this study [59] we looked for further opportunities to test our key findings on other independent data-sets. Eventually we acquired three data-sets for this purpose. In collaboration with Catarina Eira and her colleagues in Portugal and Spain we re-examined her dataset [58] on wood mice that had been sampled across four seasons from six ecologically distinct habitats on the Portuguese coast. These particular

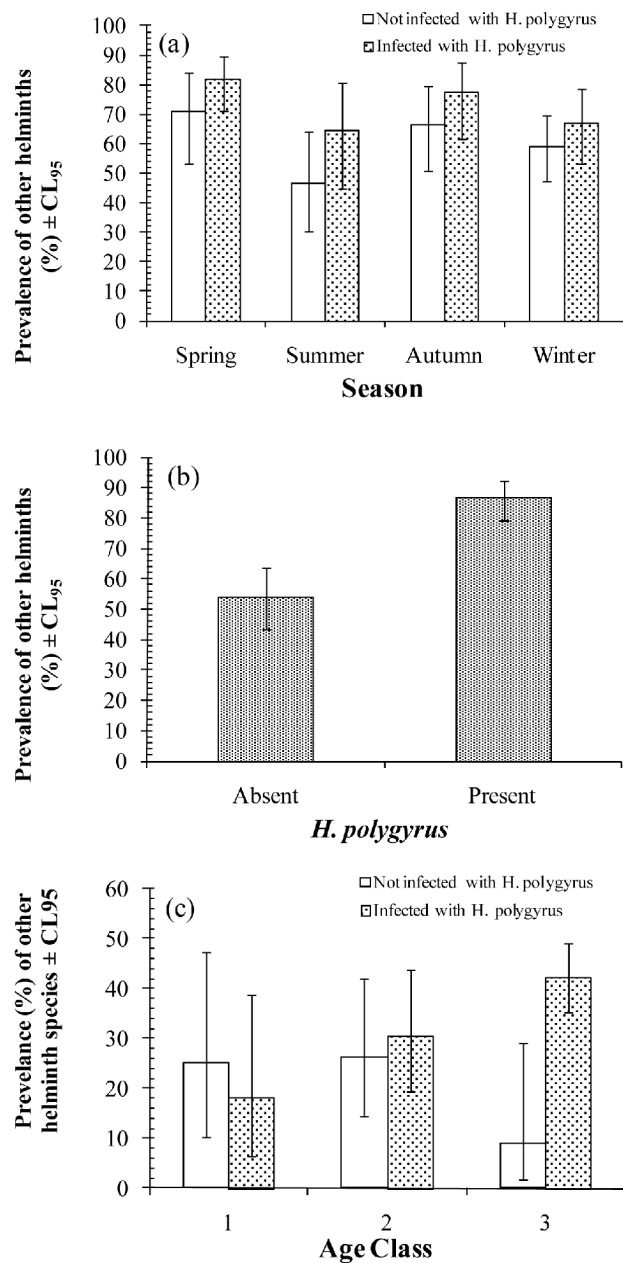


Fig. 4. Prevalence of other species of helminths in wood mice with or without *H. polygyrus*. a) Interaction with season in the Portuguese dataset; b) Unaffected by other factors in wood mice at Egham; c) Interaction with age in the Malham dataset. For further details see text and for full statistical analysis see [60]. Figure modified from [60].

populations were not infected with *C. pusilla* and no other cestode species showed a sufficiently high enough prevalence to enable us to repeat exactly the same test as that carried out on the mice from southern England. Nevertheless, the mice carried 12

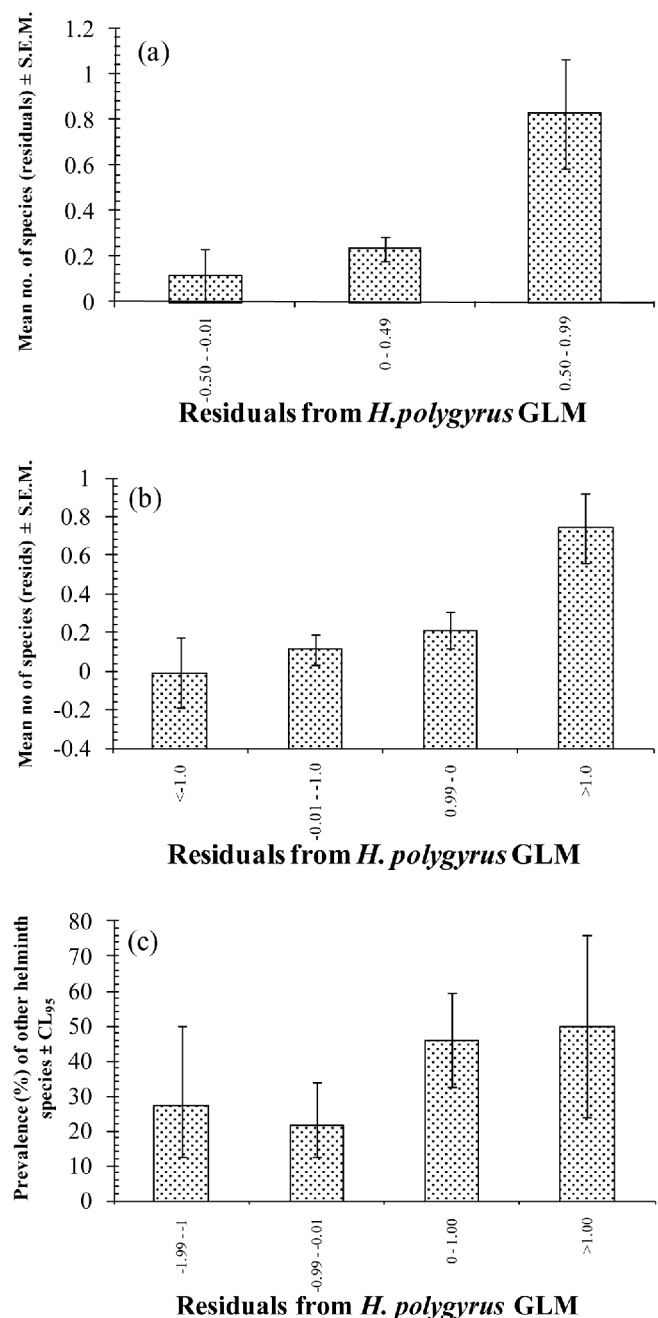


Fig. 5. Relationship between the intensity of *H. polygyrus* infection and number or prevalence of other species of helminths harboured by wood mice. The abscissas show the residuals of the *H. polygyrus* GLMs in convenient class ranges. The data are from study sites in Portugal (a), Egham Surrey U.K. (b) and Malham Tarn in Yorkshire, U.K. (c). Further details see text and [60]. Figure modified from [60].

species of helminths and therefore we tested the relationship between *H. polygyrus* and prevalence of other species, and also with species richness of other helminths [See [60] for details of the full analysis].

In this dataset 52.5% of mice without *H. polygyrus* were infected with other helminths, but the prevalence was almost 8% higher among mice with *H. polygyrus* (60.5%). There was no significant difference between the sexes in this respect, both sexes showing higher prevalence of other helminth species if they carried *H. polygyrus* as well. As Fig. 4a shows prevalence was higher in *H. polygyrus*-infected animals in all four seasons studied. (L.R. $\chi^2_3=9.43$, $P=0.024$).

As in the earlier study in S. England we detected also a significant positive relationship ($r_p=0.161$, one-tailed test, $n=178$, $P=0.016$) between the number of other helminth species and the abundance of *H. polygyrus*, after controlling for all confounding factors (i. e., differences between 6 habitats, 4 seasons, 3 age classes and both sexes). This is illustrated in Fig. 5a. Therefore, as in the earlier study, wood mice with high *H. polygyrus* infections for their particular subset, were shown to be more likely infected with other species of helminths, for their subset.

Studies on wood mice in Egham, Surrey, U.K.

Another opportunity to test the relationship between *H. polygyrus* and species richness with other helminths arose through my collaboration with John Lewis who had accumulated data over 9 years of trapping in Egham, Surrey in the U. K. This time the possible confounding factors were 9 annual datasets, 3 age classes and both sexes, but all the animals had been trapped at the same location and during the same season of each year, in late September.

Analysis of prevalence of other helminth species in these wood mice revealed a larger divergence than in the earlier studies in prevalence with other helminth species between wood mice infected (86.7%) and not infected (53.9%) with *H. polygyrus* (Fig. 4b) and this was highly significant (L.R. $\chi^2_1=23.7$, $P<0.0001$). The difference in prevalence was also marked in both sexes. In male wood mice without *H. polygyrus* the prevalence of other helminth species was 55.3% compared to 88.7% among those with *H. polygyrus*, and in females the values were very similar (50.0% versus 83.3%).

In the quantitative analysis, after controlling for all the sources of variation in data that were measured, we demonstrate again that wood mice heavily infected with *H. polygyrus* for their subset, also carried more species of other helminths for their subset ([60]; Fig. 5b; $r_p=0.24$, $n=157$, $P=0.0015$ one-tailed test).

Studies on wood mice at Malham Tarn in Yorkshire, in northern U. K.

Yet another opportunity to test the relationships between *H. polygyrus* and other helminths arose from collaboration with Mike Rogan and his colleagues at the University of Salford. They had collected data over a 12 year period on the helminths of wood mice living in the woodlands north of Malham Tarn in Yorkshire.

As in the other datasets, prevalence of other helminths was higher among mice carrying *H. polygyrus* (34.7%) compared with those without *H. polygyrus* (21.3%), a difference that was evident in both males (34.5% versus 24.3%) and females (35.1% versus 18.6%). However, age proved also to be an important factor in these animals, since the difference was most apparent in the oldest cohort of wood mice (Fig. 4c; L.R. $\chi^2_2=7.0$, $P=0.029$).

The quantitative analysis of the Malham dataset could not be undertaken in exactly the same manner as the earlier analyses because species richness was low, and only 31.1% of mice harboured helminths other than *H. polygyrus*. The maximum number of other helminth species carried by any of the mice was two, and only seven mice fell into this category. Therefore, we adopted a slightly different approach in this case. First we sorted the residuals of the *H. polygyrus* GLM into three convenient abundance classes, and for animals that were infected with *H. polygyrus* we calculated the prevalence of other helminth species in each of the three classes. As can be seen from Fig. 5c, after controlling for age, sex and year and their interactions, the prevalence of other species increased as *H. polygyrus* abundance increased ($\chi^2_1=9.8$, $P=0.002$).

Conclusions

As I explained earlier, data show clearly that interactions exist between intestinal helminths of rodents in controlled laboratory experiments, and that the strongest effects are mediated through the immune responses of the hosts [27]. However, detecting evidence for the existence of these relationships in naturally occurring wild rodent communities has been fraught with problems [16,59,61] and an important dominating role for such interactions in structuring helminth communities in wild rodents is not supported by many published studies [16,62–64]. In this paper I have tried to show that by understanding the role played by extrinsic and intrinsic factors in causing variation in parasite bur-

dens, including species richness, and by taking this into account in statistical analyses, it is possible to detect evidence for interactions. When quantified extrinsic and intrinsic patterns of variation are controlled for, patterns of co-infection compatible with synergistic interactions can be demonstrated between intestinal helminths of wood mice [16,59,60]. At least one of these, the positive relationship between *H. polygyrus* and the species richness of other helminths in wood mice has been demonstrated in four totally independent data-sets, three drawn from the U. K. and one from Portugal. It will be interesting now to determine whether similar relationships exist for other heligmosomatids infecting other rodents in Europe and in other regions, and whether any other intestinal helminths play a similar role. However, as I pointed out earlier, correlational relationships, such as those generated in the studies reviewed in this paper, can never establish unequivocally cause and effect, and the final word must await the outcome of intervention studies in which populations of parasites in wild ecosystems are manipulated experimentally (see for example [65]). Clearly, the four independent studies described in this paper show that the relationships can be observed repeatedly and, after appropriate analysis, emerge from data-sets collected in quite contrasting ecological environments distant from one another and located in different climatic zones. They are therefore robust, but even so their influence on the community structure of helminths in their hosts is still probably modest. Although they may have a role to play in the more heavily infected animals, it is unlikely that other than in exceptional circumstances, they play a decisive role in structuring helminth communities in wood mice in Europe. Nevertheless, taken together these four studies provide firm evidence that at the level of species richness, if not at the level of individual species, a highly predictable element of co-infections in wood mice has now been defined: infection with *H. polygyrus* has detectable consequence for the susceptibility of wood mice to other helminth species, particularly those associated with the intestine.

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