

Interspecies Variation in the Susceptibility of a Wild-Derived Colony of Mice to Pinworms (*Aspiculuris tetraptera*)

Ryan C Curtis,^{1,*} Jill K Murray,¹ Polly Campbell,² Yoko Nagamori,³ Adam Molnar,⁴ and Todd A Jackson¹

Pinworms are common parasites in wild and laboratory rodents. Despite their relative nonpathogenicity in immunocompetent models, pinworm infections add an unwanted variable and may confound some types of research. For this reason, health monitoring programs and biosecurity measures aim to minimize the spread of pinworm infections into colonies free from the organisms. Wild-derived and laboratory strains of mice have shown varied susceptibility to infection with *Aspiculuris tetraptera*, the most commonly found murine pinworm. In particular, susceptibility is increased in wild-derived mice, young animals, and males. Routine surveillance at our institution revealed pinworm infection (*A. tetraptera* only) within a colony of multiple, wild-derived species of *Mus*, although only specific species showed positive results during initial sampling. To assess whether species-associated differences in susceptibility were present, we analyzed fecal egg counts of *A. tetraptera* in every cage of the colony. Our results revealed significant differences in susceptibility between various species and subspecies of *Mus*. Egg counts were significantly higher in *Mus spicilegus* than *Mus m. domesticus* (WSB/EiJ) and *Mus macedonicus*. *Mus spretus* had higher egg counts than *M. m. domesticus* (WSB/EiJ), *M. m. musculus* (PWK/PhJ), and *M. macedonicus*. Egg counts did not differ in regard to age, sex, or number of mice per cage. As wild-derived mouse models continue to complement research largely based on laboratory strains, it will be important to understand host–parasite interactions and their effects on research, particularly studies evaluating immune responses, behavior, growth, and other physiologic parameters.

Pinworms are common parasites in wild and laboratory rodents. The most common pinworm detected in laboratory mice, *Aspiculuris tetraptera*, has been reported to have a prevalence of 0.19% in diagnostic samples submitted in North America.²² Mice infected with *A. tetraptera*, as well as other rodent pinworms (*Syphacia* spp.), are typically symptomless, although rectal prolapse, intestinal impaction, and mucoid enteritis have been associated with severe infestation.²⁵ Despite their relative nonpathogenicity, pinworm infections induce a Th2-associated immune response that may make infected mice unsuitable for some types of research.¹³ For this reason and because of other potential effects, health monitoring programs and biosecurity measures aim to minimize the spread of pinworm infections to pinworm-free colonies.

The prevalence of *A. tetraptera* in wild mouse populations is unknown, however it is likely much higher than in laboratory populations of mice. Susceptibility has been measured in wild-derived mice, as estimated by their parasite burdens, and is highly variable. This has been shown in both naturally occurring and experimental infections of house mice (*Mus musculus*) with *A. tetraptera*.^{19–21,23} Laboratory mouse strains, in comparison to wild-derived mice, are much more resistant to infection. Selective pressures of laboratory breeding and husbandry over time could potentially cause resistant genetic associations to be favored.⁷ A number of studies have also

illustrated that young mice and males are more susceptible to pinworm infections.^{1,2,4,5,16,17}

During routine health surveillance at our institution, *A. tetraptera* was discovered in an investigator managed colony of wild-derived mice. Although a number of species and subspecies of the genus *Mus* are housed within the colony, initial testing by cecal–colon contents examination revealed positive results only in certain species. As the original samples tested only represented a subset of the entire colony, further investigation was needed. Based on our initial findings and from previous work within *M. musculus*, we hypothesized that susceptibility to infection with *A. tetraptera*, as estimated by parasite burden, would be species- or subspecies-dependent.

Materials and Methods

Description of mouse colony. Mice sampled in this study represented 6 wild-derived inbred strains representing 4 closely related species in the genus *Mus*—*Mus spretus*, *Mus spicilegus*, *Mus macedonicus*, and 2 subspecies of the house mouse, *M. musculus* (*M. m. musculus* and *M. m. domesticus*). With the exception of the 2 *M. m. domesticus* strains, wild-caught founders were from the native range of each species in the Old World. The *M. spretus* strain (SFM) is from Montpellier, France; the *M. spicilegus* strain (ZRU) is from the Ukraine, and the *M. macedonicus* strain (XBS) is from Bulgaria. All 3 strains were developed by the Montpellier Wild Mice Genetic Repository (Montpellier, France). Of the mice used in this study, *M. spicilegus* and *M. macedonicus* breeding colonies were established with mice purchased directly from the Montpellier facility, whereas *M. spretus* breeding pairs were a gift from Jeffery Good (University of Montana). The *M. m. musculus* strain, PWK/PhJ, was derived from populations in the Czech Republic;^{12,24} the 2 *M. m. domesticus* strains, LEWES/EiJ

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¹Animal Resources Unit, Division of the Vice President for Research; ²Department of Integrative Biology, College of Arts and Science; ³Department of Veterinary Pathobiology, Center for Veterinary Health Sciences; and ⁴Department of Statistics, College of Arts and Sciences, Oklahoma State University, Stillwater, Oklahoma.

*Corresponding author. Email: Ryan.Curtis@okstate.edu

and WSB/EiJ, were derived mice from Delaware and Maryland, respectively (<https://www.jax.org/>). North American populations of *M. m. domesticus* are part of the recent global expansion of this subspecies from its native range in Western Europe. The 4 house mouse strains were purchased from Jackson Laboratory (Bar Harbor, ME). All strains have been maintained under laboratory conditions for at least a decade.

Husbandry procedures. The mouse colony used in this study was maintained on a 12:12-h light:dark cycle in a single large room (574 ft²) in the Non-Centralized Animal Facility of the Department of Integrative Biology at Oklahoma State University (Stillwater, OK). Mice were housed in either standard (7.5 × 11.5 × 5 in.) or large (10.5 × 19 × 6.125 in.) polycarbonate mouse cages, bedded with woodchip bedding (Sani-chips, PJ Murphy Forest Products, Monvale, NJ). Cages were topped with wire-bar lids only (that is, no microfilter tops). Tap water and chow (Laboratory Rodent Diet 5001, LabDiet, St Louis, MO) were provided without restriction. Strains were grouped together on open metal racks but were not otherwise separated from each other. Cages were changed weekly and were sanitized in a mechanical cage washer. Pups were weaned into same-sex groups at 21 to 28 d. Male *M. spretus* and *M. macedonicus* mice were separated before 6 wk to avoid aggression, and all other strains were maintained in same-sex groups (maximum 4 adults per cage) or in breeding pairs. Some of the mice sampled in this study had been used in nonaversive behavioral assays (for example, conditioned place-preference and open-field tests). A health monitoring program was in place, and comprehensive PCR screening resulted in positive detection of pinworms (*A. tetraoptera* only), *Helicobacter* spp., and murine norovirus. None of the mice had been treated for, or had known exposure to, any pathogen. All animal procedures and experiments with these mice were completed under a protocol approved by the Oklahoma State University IACUC.

Sampling technique and experimental design. Fecal samples were collected from all 139 cages of the colony immediately after routine cage-change procedures. Approximately 1 g (20 fecal pellets) of fresh feces was collected from multiple locations within each cage. Gloves were changed between cages. Samples were placed in sterile vials, labeled, refrigerated (4 °C), and analyzed within 24 h of collection.

Fecal egg counts. Fecal egg counts (eggs per g) were performed by a clinical parasitologist who was blinded in regard to mouse species and subspecies. The Wisconsin egg-counting test²⁸ was used to analyze samples. Each of the fecal samples was weighed (Harvard Trip balance, Ohaus, Parsippany, NJ) to approximately 1 g, soaked in a few drops of water until soft, and mixed with Sheather sugar solution (454 g granulated sugar in 355 mL water). The mixture was strained by a tea strainer and poured into a 15-mL centrifuge tube (Fisherbrand, Pittsburgh, PA) until a slight inverse meniscus was formed. A coverslip (Fisherbrand) was placed on top of the tube, which was spun in a CL2 centrifuge (ThermoScientific, Pittsburgh, PA) for 5 min at approximately 1500 rpm (~approximately 182 × g). The coverslip was removed and placed on a glass slide (Fisherbrand) for examination under a binocular microscope (Olympus, Center Valley, PA) at 100× magnification. The number of *A. tetraoptera* eggs was counted by using a hand tally counter (VWR, Rander, PA) and recorded. The maximum number of eggs used for data was capped at 1000 eggs per g.

Statistics. All data and analyses used the cage as the experimental unit. There was a total of 275 mice: 64 cages held 1 mouse, 54 had 2 mice, 11 had 3 mice, 6 had 4 mice, 3 had 5 mice, and 7, 8, 9, and 10 mice were present in one cage each. Fecal

egg counts were compared between species and subspecies by using the Kruskal–Wallis test (due to unequal variance) and the Dunn posthoc test. In addition, an exploratory regression model was constructed to evaluate other possible predictors of pinworm susceptibility (R Statistical Package, version 3.2.4, Vienna, Austria). Differences with a *P* value less than or equal to 0.05 were considered significant. Confidence intervals for proportions were computed as Clopper–Pearson exact confidence intervals, because some subspecies of mice had cell counts of 5 or less. Student *t*-distribution confidence intervals for means were truncated to 0 when necessary because pinworm counts cannot be negative. An analysis was considered to be significant when the 2-tailed *P* value was less than or equal to 0.05.

Results

Interspecies variation in susceptibility. Six species and subspecies of mice in the colony were sampled, which came from sources as previously described. There were 3 subspecies of *M. musculus*—*M. m. musculus* (PWK/PhJ; 13 cages), *M. m. domesticus* (WSB/EiJ; 19 cages), and *M. m. domesticus* (LEWES/EiJ; 11 cages). The other 3 species present were *M. macedonicus* (12 cages), *M. spicilegus* (35 cages), and *M. spretus* (49 cages). The prevalence of *A. tetraoptera* pinworm infection, confirmed by positive fecal analysis, is shown in Table 1. A χ^2 test provided evidence suggesting at least one statistically significant effect ($\chi^2 = 28.49$ at 5 degrees of freedom, $P < 0.001$). Comparing confidence intervals for overlap indicated that pinworm prevalence was significantly higher in *M. spretus* than *M. macedonicus* or *M. m. domesticus* (WSB/EiJ).

To examine differences between subspecies more closely, the numeric distribution of pinworm eggs per gram by species and subspecies was examined. Boxplots (Figure 1) of egg counts (no. of eggs per g feces) by subspecies show a distribution that is right-skewed for all groups. Summary statistics and 95% confidence intervals appear in Table 2. Figure 2 illustrates sample means and 95% confidence intervals for each species and subspecies. Visually, the confidence intervals for *M. spicilegus* and *M. spretus* were separated from the intervals for *M. macedonicus* and all subspecies of *M. musculus*. Group means were compared by using the Kruskal–Wallis test. Means differed significantly by group ($\chi^2 = 38.30$ on 5 degrees of freedom, $P < 0.001$). The post hoc Dunn test, conducted with the Bonferroni adjustment for multiple comparisons with a family-wise error rate of $\alpha = 0.05$, mostly matched the visual evidence. The mean for *M. spicilegus* was significantly different from those for *M. m. domesticus* (WSB/EiJ; $P < 0.001$) and *M. macedonicus* ($P = 0.001$). The mean for *M. spretus* was significantly different from those for *M. m. domesticus* (WSB/EiJ; $P < 0.001$), *M. m. musculus* (PWK/PhJ; $P = 0.003$), and *M. macedonicus* ($P < 0.001$).

Sex-associated resistance. Of the 139 cages, 33 contained female mice only, 61 contained male mice only, and 45 contained both male and female mice. Because prior research had identified higher pinworm prevalence in male mice, cages with female mice only were compared with cages containing male mice only. Of the 33 female-only cages, 20 (60.6%; 95% confidence interval [CI], 42.1% to 77.1%) had eggs; of the 61 male-only cages, 40 (65.6%; 95% CI, 52.3% to 77.3%) had eggs. This difference was not statistically significant (Fisher exact test $P = 0.69$). Examining pinworm counts revealed slightly more disparity. Female-only cages averaged 59.30 ± 106.16 (mean \pm 1 SD; 95% CI, 21.66 to 96.95) eggs per gram, whereas male-only cages averaged 138.30 ± 227.83 (95% CI, 79.94 to 196.65) eggs per gram. Under the Kruskal–Wallis test for nonnormal distribution, the difference

Table 1. Cage prevalence of pinworm infection by species or subspecies

	No. of cages	Pinworm-positive cages		
		No.	%	95% CI
<i>M. m. domesticus</i> (LEWES/EiJ)	11	7	63.6	30.8% to 89.1%
<i>M. m. domesticus</i> (WSB/EiJ)	19	5	26.3	9.1% to 51.2%
<i>M. m. musculus</i> (PWK/PhJ)	13	6	46.2	19.2% to 74.9%
<i>M. macedonicus</i>	12	4	33.3	9.9% to 65.1%
<i>M. spicilegus</i>	35	24	68.6	50.7% to 83.1%
<i>M. spretus</i>	49	42	85.7	72.8% to 94.1%
Total	139	88	63.3	54.7% to 71.3%

between groups was not statistically significant ($\chi^2 = 1.38$ on 1 degree of freedom, $P = 0.241$).

Exploratory regression model. To further investigate potential predictors of pinworm susceptibility, an exploratory regression model was constructed by using data collected during the fecal egg collection. Each cage had the following 5 potential predictor variables: species or subspecies, number of mice, sex (both male and female as a dichotomous variable), and age (defined as mean age). As mentioned earlier, eggs per gram had a right-skewed distribution and could not be negative. Eggs per gram also had increasing variance. Therefore, the response variable in the model was the natural logarithm of (eggs per gram + 1), which kept cages without pinworms at 0 and reduced the

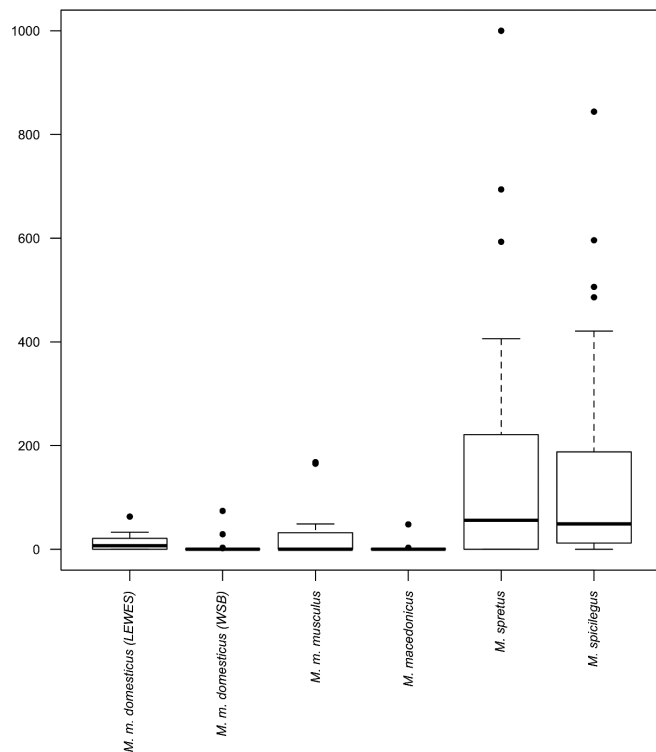


Figure 1. Descriptive statistics. A box plot depicts the raw data of fecal egg counts by mouse species or subspecies.

Table 2. Summary statistics for fecal egg count data

	<i>n</i>	Mean \pm 1 SD	95% CI
<i>M. m. domesticus</i> (LEWES)	11	14.36 \pm 20.02	0.91 to 27.81
<i>M. m. domesticus</i> (WSB)	19	5.74 \pm 17.80	0 to 14.32
<i>M. m. musculus</i> (PWK)	13	34.85 \pm 60.57	0 to 71.45
<i>M. macedonicus</i>	12	4.42 \pm 13.75	0 to 13.16
<i>M. spicilegus</i>	35	168.77 \pm 269.41	76.23 to 261.32
<i>M. spretus</i>	49	139.53 \pm 189.75	85.03 to 194.03
Total	139	97.24 \pm 188.57	65.62 to 128.87

skewness of nonzero counts. For this exploratory model, this transformation was sufficient; all fitted values were positive. Residual analysis indicated no multicollinearity and acceptable residuals.

The regression model yielded $R^2 = 0.3033$. Table 3 contains the coefficient estimate, standard error, *t* test statistic, and *P* value for each predictor. Coefficients for mouse species or subspecies are presented as indicators against the reference case of *M. spretus*. Examining the categories of species/subspecies together, a partial F test was highly significant ($F_{5,129} = 10.4768$, $P < 0.001$). These results aligned with the earlier analyses of species-, subspecies-, and sex-associated effects; the intercept and mouse species or subspecies were statistically significant, but no other predictor was significant.

Discussion

Our study demonstrated significant differences in susceptibility to pinworm (*A. tetraaptera*) infections depending on the mouse species or subspecies sampled. *M. spicilegus* and *M. spretus* showed the highest susceptibility to pinworm infection. Note

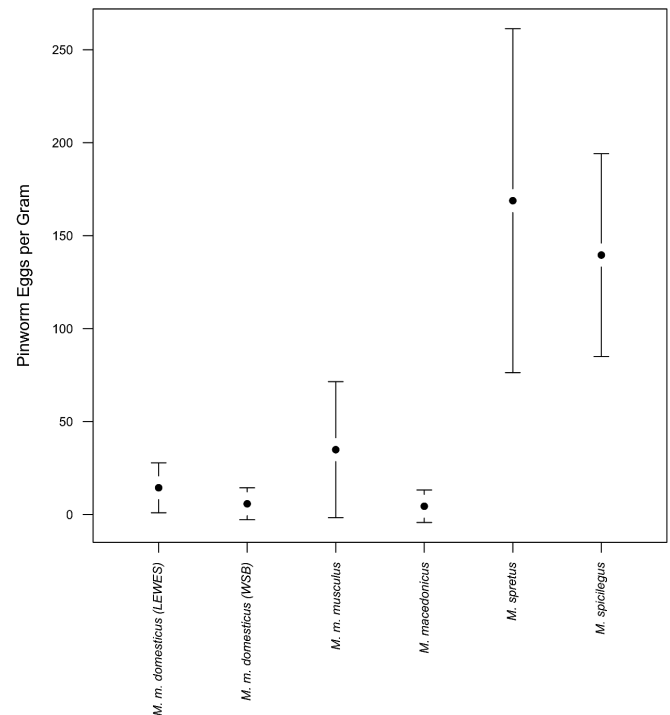


Figure 2. Pinworm egg counts (per g feces; mean \pm 1 SD). Egg counts were higher in *M. spicilegus* than *M. m. domesticus* (WSB) and *M. macedonicus* and in *M. spretus* than in *M. m. domesticus* (WSB), *M. m. musculus* (PWK), and *M. macedonicus*.

Table 3. Regression model

Predictor	Estimate	SE	<i>t</i>	<i>P</i>
Intercept	3.895	0.593	6.564	<0.001
Number of mice	-0.088	0.127	-0.692	0.490
Female indicator	-0.289	0.474	-0.610	0.543
Male indicator	-0.087	0.507	-0.173	0.863
Age (d)	0.0021	0.0017	1.223	0.224
<i>M. m. domesticus</i> (LEWES)	-2.244	0.728	-3.081	0.003
<i>M. m. domesticus</i> (WSB)	-3.421	0.590	-5.793	<0.001
<i>M. m. musculus</i> (PWK)	-2.126	0.697	-3.052	0.003
<i>M. macedonicus</i>	-3.201	0.662	-4.837	<0.001
<i>M. spicilegus</i>	-0.719	0.492	-1.460	0.147

that all colony mice are expected to have similar exposure, given that all mice are conventionally housed in open-top (no filter top) cages, as previously described. Nearly 1 y had passed since the initial colony screening and experimental survey, ultimately leading to an established colony infestation. No procedures are in place to reduce the risk of any type of exposure between species or subspecies. The use of filter tops alone has been shown to dramatically reduce pinworm transmission within a colony.²⁶ Previous reports in *M. musculus* have shown increased susceptibility in male and younger mice.^{4,5,16,17} However, we failed to show significant differences in susceptibility according to age, sex, or number of mice in the cage.

Resistance to pinworm infection appears to be most influenced by host species or strain identity. Both inbred and outbred laboratory strains are much more resistant to pinworm infections than are wild mice.⁷ The authors of the cited study propose that increased parasite exposure and opportunity for reinfection in captive mouse colonies has selected for pinworm-resistant laboratory mice.⁷ The strains examined in our current study, although wild-derived, have been maintained in laboratory settings for many generations. Therefore, parasite-mediated selection for resistance in laboratory compared with wild mice cannot explain the large strain and species differences in pinworm infections resistance reported here. We propose 2 nonmutually exclusive explanations for this result. First, the low susceptibility of house mouse strains relative to *M. spretus* and *M. spicilegus* may reflect a history of strong selection for parasite resistance in natural populations of house mice, which live at high densities relative to noncommensal congeners.¹¹ Second, the decreased susceptibility of inhouse mouse strains may reflect the many generations of strong artificial selection against infection-prone mice at the vendor facility, which practices rigorous health monitoring from which pinworms are excluded (<https://www.jax.org/jax-mice-and-services/customer-support/animal-health/list-of-agents-monitored>; Table 1). We note that neither explanation is consistent with the very low rate of infection detected for *M. macedonicus*, a noncommensal species from a facility without intensive monitoring for nonpathogenic parasites. Ultimately, discriminating the contributions of natural variation in susceptibility from differential exposure to artificial selection in the lab will require experimentally infecting the strains sampled in the current study as well as wild-caught progenitors.

Our colony survey had several limitations. The diagnostic technique we used, fecal flotation method, is not the most sensitive test for the detection of pinworms. Evaluation of cecal–colon contents remains the ‘gold standard’ for pinworm detection,¹⁰ and newer real-time PCR techniques demonstrate greater sensitivity than do traditional antemortem methods.⁸ We did not

assess cecal–colon contents, because this evaluation can only be done postmortem, and we did not use PCR methods because they cannot reveal relative severity of infection according to parasite burden. The 2 remaining convenient and widely used methods for antemortem testing include tape testing and fecal flotation. We used fecal flotation methods in our study because *A. tetraptera* eggs are deposited in the lumen of the colon.⁹ Therefore, fecal flotation was the best available approach for detecting severity of infection antemortem.

Biomedical research typically involves classic, inbred mouse strains for work requiring a mammalian model. Although these strains have many advantages (for example, high fecundity, docility, and availability of disease-specific models) they are limited in terms of genetic and phenotypic diversity. In contrast, wild-derived mouse strains are collectively genetically heterogeneous and are characterized by greater behavioral and physiologic diversity than are standard laboratory strains. As such, wild-derived mouse models are complimentary to classic inbred strains and are important in many areas of research, including aging, virology, immunology, ecotoxicology, and cancer genetics.^{3,6,14,15,18,27}

In conclusion, our current study demonstrates increased susceptibility to pinworm infections in some species and subspecies within a colony of wild-derived mice in the genus *Mus*. Given that the use of wild-derived mouse models is likely to increase, it is important to understand host–parasite relationships between the most commonly used animal model and a common parasite. In addition, parasite burden and susceptibility must be evaluated as a research variable, with its effect on specific biologic systems. Further work is necessary to ultimately uncover the effect of these parameters on immune responses, behavior, and growth.

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