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Original Article

Social context alters host behavior and infection risk

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Variation in infection risk and transmission potential are widespread in human and wildlife diseases and play a central role in host–pathogen dynamics. To explain this variation, most studies focus on linking host traits to differences in pathogen exposure, infection, and transmission, but typically do not account for hosts' social context. Yet, an individual's risk of acquiring infection is likely influenced jointly by their own traits and their social environment. Here, we use 3 natural genotypes of the fruit fly *Drosophila melanogaster* to test how variation in pathogen transmission is linked to differences in host behavior and social context. We constructed groups of 12 flies from 1 of 3 different genotypes and 5 different sex ratios (0%, 33%, 50%, 67%, or 100% female) in a fully factorial design. To each group, we added a male or female "primary case" fly that had been exposed to the generalist fungal entomopathogen *Metarhizium robertsii*. We then recorded groups' aggregation behavior, mating frequency, and infection prevalence. Aggregation and mating behavior were influenced either jointly or additively by fly genotype and sex ratio. However, a combination of individual-level (mating history; the sex of the primary case) and group-level factors (sex ratio) jointly influenced individuals' infection risk. There were more infections in female-biased groups, though the sex of the primary case also influenced sex-biased mortality and the relationship between individuals' mating history and infection risk. Thus, an individual's social environment can be an important predictor of social dynamics and their survival outcomes.

Key words: **host behavior, host genotype, infection risk, sex ratio, social context.**

INTRODUCTION

Heterogeneities among hosts in their infection risk and potential for transmission are widespread in human and wildlife diseases and play a key role in the ecological and evolutionary dynamics of host–pathogen systems (Dwyer et al. 1997; Woolhouse et al. 1997). To explain this heterogeneity, previous studies have largely focused on host traits (Martin et al. 2016). For instance, differences among hosts in their size (Saad-Fares and Combes 1992), behavioral tendencies (Barron et al. 2015), and immunocompetence (Gopinath et al. 2014) can have drastic consequences for disease outcomes. However, the risk of an individual becoming infected will be a function of their own traits and their social context, that is, the number and types of conspecifics with whom the host interacts (Salje et al. 2016). The dynamics of many directly transmitted diseases are dependent on social encounters among conspecifics, and the frequency of encounters is contingent on factors of social context, like group size (Nunn et al. 2015), phenotypic composition (Farine et al. 2015), and social organization (Altizer et al. 2003). Studying individuals' traits in isolation, therefore, may be a less powerful predictor of disease dynamics relative to more comprehensive analyses including social context. For horizontally transmitted pathogens, identifying important modes of transmission (e.g., social contact, sex, antagonistic interactions) and the individual-level and group-level factors which influence the frequency of these events is an important step in predicting epidemiological dynamics.

One important factor of the social environment with consequences for pathogen transmission is the group's sex ratio. Individuals will alter their aggregation tendencies and reproductive decision making in response to the sex ratio they experience (Ah-King and Gowaty 2016). Thus, the sex ratio can determine the contact network of individuals within a group (i.e., who interacts with whom) and thereby determine disease transmission patterns. Even in populations with equal sex ratios, individuals aggregate non-randomly and group sex ratios can vary broadly. For example, in over 40 primate species with mostly equal birth sex ratios, the sex ratios in social groups vary from roughly equal to over 90% female (Clutton-Brock et al. 1977). In many social animals, both males and females aggregate preferably with females (e.g., guppies, Brask et al. 2011; fruit flies, Lindström and Ranta 1993; Foley et al. 2015). Irrespective of the causes behind differences in group sex ratio, the consequences of sex ratio bias can be far-reaching: the minority sex can become choosier (e.g., Berglund 1994; Pollet and Nettle 2008), average reproductive success can fluctuate (Souroukis

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and Murray 1994; Rotenberry et al. 2016), and sex-biased mortality may arise or shift direction (Zuk 1990; Vicente et al. 2007). Taken together, groups with a certain set of characteristics (e.g., a female biased sex ratio) may experience greater aggregation and mating potential with a concomitant increase in the risk of infectious diseases (Thrall et al. 1997).

Another related aspect of the social environment that will influence individuals' relative risk of acquiring infections is the sex of the infectious individual(s) in the social group. Many directly transmitted infectious disease outbreaks begin with a single individual contracting an infection (i.e., the "primary case") and the number of secondary infections that they generate will depend, in part, on their own behavioral tendencies (e.g., promiscuity, Eames and Keeling 2002) and their pool of potentially receptive mates (Adimora and Schoenbach 2005). For example, the spread of sexually transmitted infections may be delayed depending on the sex of the primary case (Downs and De Vincenzi 1996) or increased in social groups that engage in a greater frequency of sexual encounters (Liljeros et al. 2003). The consequences of different group sex ratio may also be more pronounced in systems where sexes differ in disease susceptibility. Sex-differences in disease risk are widespread (Zuk and McKean 1996; Duneau et al. 2012; Gipson and Hall 2016), and males are often more susceptible than females (Zuk 2009), so infection risk is likely a product of individual traits (e.g., sex, behavioral tendencies, etc.) and factors of the social environment (e.g., sex ratio). However, these factors may be confounded in observational studies and their relative effects on disease dynamics are rarely tested in unison.

Here, we use the fruit fly *Drosophila melanogaster* and the generalist entomopathogenic fungus *Metarhizium robertsii* as a model host–pathogen system to test how host genotype, group sex ratio, and the sex of the primary infected individual can influence aggregation behavior, mating dynamics, and individual infection risk. We also test how aggregation and mating behavior changed in the presence of an infectious conspecific compared to unexposed controls. In general, aggregating with conspecifics and mating represent 2 common routes of horizontal pathogen transmission (Loehle 1995). Thus, we hypothesize that groups with more aggregation and mating will experience a greater prevalence of infection. Together, these experiments allow us to disentangle the relative importance of host traits vs. social context influencing patterns of disease.

MATERIALS AND METHODS

Fly genotypes and maintenance

Drosophila melanogaster represents a valuable model system to test these questions because replicate genotypes can be reliably produced in the laboratory, different genotypes are known to vary in their space use (Stamps et al. 2005), and social group preferences (Saltz 2011; Saltz and Foley 2011; Saltz 2017), and individuals can acquire and transmit pathogens during mating (Miest and Bloch-Qazi 2008; Zhong et al. 2013). Flies used in this experiment were heterozygous F1 offspring of inbred parental lines obtained from the *Drosophila* Genetics Reference Panel (DGRP2.gnets.ncsu.edu; Mackay et al. 2012), originally collected from a population in Raleigh, NC. The direction of the crosses (i.e., maternal and paternal genotypes) was consistent to control for maternal effects. That is, genotype "A/B" would be generated by crossing virgin females of genotype A to males of genotype B and collecting their virgin F1 offspring. We used 3 genotype crosses previously shown to vary in social behaviors (Saltz 2011, 2013; Stamps et al. 2013; Saltz 2017): 315/365, 306/391, and 732/774. These genotypic differences in social behavior are context-dependent and influenced by the social environment (e.g., group size; Saltz 2011). Thus, this system is well suited to test the relative contributions of host traits and social environments on individual infection risk. Experimental F1 flies were collected as virgins twice a day for 72 h.

Experimental pathogen exposure

We used the generalist entomopathogenic fungus *Metarhizium robertsii* as a model pathogen because it is infectious and virulent in *D. melanogaster*, drastically reducing host lifespan and fecundity (McClure et al. 2014; Hunt et al. 2016), and its mode of transmission is primarily via sexual contact (Zhong et al. 2013). *Metarhizium robertsii* is a common soil fungus worldwide (Bidochka et al. 2001; Roberts and St Leger 2004) that infects arthropod hosts via conidiospores adhering to the cuticle and penetrating directly into the hemolymph (Wang et al. 2016). This strain (ARSF# 2576) was originally obtained from the USDA-ARS Collection of Entomopathogenic Fungi Cultures in Ithaca, New York, USA. Fungal cultures were grown for 3 weeks on Sabouraud Dextrose Agar before collecting conidiospores by using an inoculating loop to scrape dark green conidia from the surface of a sporulating *M. robertsii* culture into a sterile vial. We topically exposed primary case flies to conidia by transferring each fly individually into a vial containing 1.5 mg of infectious conidia and moving them directly back into their rearing vial using a sterile fine paintbrush (similar to methods in Hunt et al. 2016). After this process, flies were visibly covered in conidia and immediately began grooming. Flies were left in isolation and allowed to groom for 24 h to recover before the onset of mating trials. In a series of preliminary experiments, we verified that this strain of *M. robertsii* can be transmitted among individuals via mating and indirectly via the environment, and also found evidence that the fly genotypes used in this experiment differ in susceptibility to disease-induced mortality (measured by the time to death after infection; see Supplementary Materials for details).

Aggregation, mating frequency, and infection across social contexts

Virgin flies were collected as described above and maintained in isolation for 10 days before social group construction. Three days before social groups were formed, we painted each fly with a unique color ID atop their dorsal thorax using modeling paint. About 24 h before groups were formed, a subset of flies was selected haphazardly from each genotype and exposed to *M. robertsii* conidia as described above and then placed back into their housing vial. These exposed flies would serve as the primary infection cases for experimental transmission events within social groups. At 09:00 h, the following morning, we formed social groups of 12 flies in 1 of 5 sex ratios: all females (n = 8 groups), 4 males and 8 females (n = 10 groups), 6 males and 6 females (n = 11 groups), 8 females and 4 males (n = 9 groups), or all males (n = 10 groups). Each group contained flies of the same genotype that were collected within the same 24 h period. Groups of different sex ratios were formed for each genotype in a fully factorial design; half of each genotype × sex ratio combination received a single female primary case (n = 25) and the other half received a single male primary case (n = 23) of the same genotype as the unexposed flies in their group. After the exposed fly was added, the social groups contained 13 individuals.

Flies were moved into their groups after spending ~3 min in a −20°C freezer to limit movement during transportation. Since most social interactions, courtship, and mating take place on or near

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food sources in *D. melanogaster* (Harshman et al. 1988; Wertheim et al. 2002), groups were housed in inverted plastic petri dishes (diameter = 13.5 cm, height = 2 cm) containing a smaller petri dish (100 mm diameter) filled with grapefruit juice agar as a food patch (see supplementary material for details). Every 5 min for 60 min, we noted the number of flies aggregating on the food patch and noted the identities of any flies engaged in mating. Mating in *D. melanogaster* takes ~13–20 min, so it is unlikely that we missed any mating events. After 60min, all flies were CO_2 anesthetized and each fly was moved back to its rearing vial. We repeated this process the following morning, so each social group interacted for a total of 2 h across 2 days. After the completion of social group observations, flies were maintained in isolation in rearing vials until they died, after which we checked for infection status by sterilizing the cadaver's outer body surface and placing them on wetted sterile filter paper to verify fungal growth through the cuticle (e.g., Figure 3C; following protocols in Lacey 1997). This method did not allow us to detect whether individuals had become infected and then recovered. We also constructed a set of control groups of 13 flies with the same characteristics as above, but the primary case was instead exposed to non-infectious conidiospores that were autoclaved for 20 min at 121°C. We allowed these groups to interact as before and recorded the same values to compare the average number of flies on the food patch and the total number of mating events across social groups with control and infectious primary cases. The experiment was conducted in 2 blocks, December 2016 and March 2017.

Statistical analyses

For all statistical models, we originally included all pairwise interaction terms between independent variables, but non-significant interaction terms were removed for model simplification (Crawley 2012). The simplified models are presented here. We excluded 3-way interactions because of insufficient replication to detect these effects (Heo and Leon 2010). Aggregation data (the number of flies present on the food patch at each time point) were analyzed with a generalized linear mixed model (GLMM) with a beta binomial error distribution and a logit link function (goodness of fit: $\chi^2 = 900.1$, $P = 0.45$) with the following independent variables: genotype, group sex ratio, primary case sex, and a genotype × sex ratio interaction term. Block ID and observation time point nested in group ID were included as random effects to account for the non-independence of measurements across time points. The total number of mating events observed were analyzed with a GLMM with a Poisson error distribution and a log link function with the following independent variables: genotype, group sex ratio, and primary case sex. Groups containing only flies of 1 sex and primary case of the same sex were excluded from the analysis of mating frequency, because we observed no same-sex mating events in any of these groups. Individual risk of infection was analyzed using a binary logistic regression (infected = yes/no) with the following independent variables: sex, mating history (i.e., number of mating events), genotype, group sex ratio, sex of primary case, individual sex × primary case sex, and mating history × primary case sex. Block ID and individual ID nested in group ID were included in the model as random effects. Comparisons of patch-use and mating frequency among treatments (i.e., groups with and without an infectious fly present) were performed with GLMMs with beta binomial and Poisson distributions, respectively. We included time point nested in group ID as a random effect. All statistical analyses were performed in JMP Pro version 12.1.

RESULTS

Aggregation and mating frequency across social contexts

Aggregation behavior was influenced jointly by fly genotype and group sex ratio (interaction term: $\chi^2 = 63.86$, df = 8, $P < 0.0001$; Table 1; Figure 1A). On average, flies aggregated over 2.2 times more in male-biased groups, though 1 genotype deviated from this trend. The number of flies aggregating on the food patch also increased over time (estimate = 0.08, SE = 0.008, 95% CI = 0.0641–0.0952). The sex of the primary case had no effect on aggregation behavior ($P = 0.28$, Table 1). On average, we observed 60% fewer flies present on the food patch when there was an infectious fly present compared to control groups where the primary case was exposed to non-infectious autoclaved spores ($\chi^2 = 33.19$, df = 1, $P < 0.0001$; Figure 1B).

The number of mating events observed in social groups was influenced additively by host genotype ($\chi^2 = 6.21$, df = 2, $P = 0.04$; Figure 2B) and group sex ratio ($\chi^2 = 30.06$, df = 4, $P < 0.0001$; Figure 2A). On average, 1 genotype (306/391) engaged in 70% more mating events than another (315/365), while the third genotype (732/774) exhibited an intermediate value. Groups containing 12 male or 12 female flies with a primary case of the opposite sex experienced 3 times fewer mating events than intermediate sex ratios, with female-biased groups experiencing the most mating events. The sex of the primary case had no effect on mating frequency ($P = 0.66$, Table 1). We observed no difference in the number of mating events occurring in social groups with or without an infectious fly present ($\chi^2 = 0.59$, df = 1, $P = 0.44$).

Group incidence of fungal infection

We found no evidence that host genotype predicted infection risk ($P = 0.87$; Table 1). Rather, infection risk was only predicted by group-level characteristics and their interactions with individual factors. Infection varied among groups with different sex ratios ($\chi^2 = 18.09$, df = 4, $P = 0.001$; Table 1; Figure 3A), where infection prevalence was greatest in groups that were intermediately female-biased. In determining individual infection risk, there was a significant interaction between the sex of the primary case and the sex of the focal fly

Table 1

Results of generalized linear models predicting patch use, the number of mating events, and infection-associated mortalities in social groups. Significant effects are denoted with asterisks.

Effect	df	χ^2 value	*P*-value
Patch-use			
Genotype	2	26.90	<0.0001*
Sex ratio	4	55.16	<0.0001*
Sex of primary case	1	1.34	0.28
Genotype × sex ratio	8	63.86	<0.0001*
Mating frequency			
Genotype	2	6.21	0.04*
Sex ratio	4	30.06	<0.0001*
Sex of primary case	1	0.19	0.66
Individual risk of infection			
Sex	1	2.31	0.13
Mating history (# mating events)	1	0.86	0.35
Genotype	2	0.28	0.87
Sex ratio	4	18.09	0.001*
Primary case sex	1	4.85	0.03*
Sex × primary case sex	1	9.55	0.002*
Mating history × primary case sex	1	4.52	0.03*

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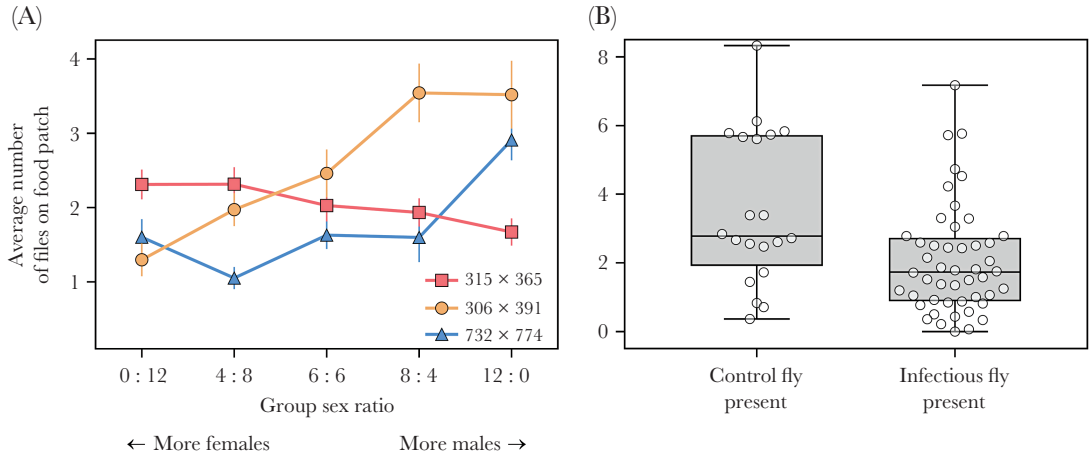

Figure 1
Aggregation behavior across different social contexts. (A) On average, aggregation increased with more male-biased groups. However, one genotype deviated from this trend. Vertical bars represent standard error of the mean. (B) We observed 60% fewer flies present on the food patch when there was an infectious fly present compared to groups where the primary case was exposed to non-infectious conidiospores. Boxplots extend from the 25th to 75th percentiles, with median represented by the middle horizontal line. Vertical lines extend to the minimum and maximum values.

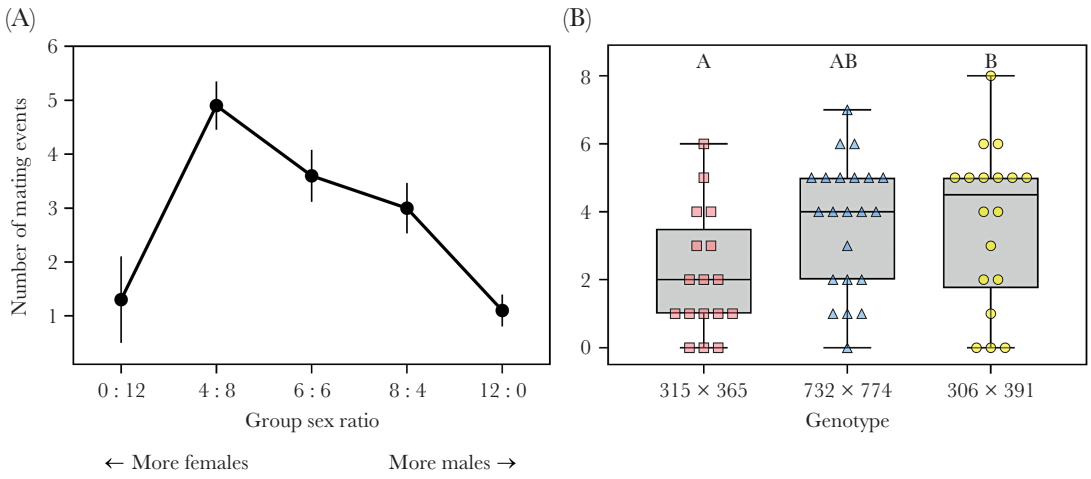

Figure 2
Mating frequency across different social contexts and fly genotypes. (A) The number of mating events observed in social groups was the lowest in groups composed only of one sex (with an primary case of the opposite sex), and greatest in intermediately female-biased groups. (B) Fly genotypes varied in the number of mating events observed in social groups. Boxplots extend from the 25th to 75th percentiles, with median represented by the middle horizontal line. Vertical lines extend to the minimum and maximum values.

(χ^2 = 9.55, df = 1, P = 0.002; Table 1; Figure 3B). Males in groups with a female primary case experienced 4 times the prevalence of infection compared to females, but the risk of infection did not differ between males and females when the primary case was male.

Overall, we found that 17% of mated flies became infected in our social groups, whereas only 10% of virgin flies became infected, indicating some non-sexual transmission. There was a significant interaction between a fly's mating history and the sex of the primary case (χ^2 = 9.55, df = 1, P = 0.002; Figure 3D; Table 1). In social groups where the primary case was male, flies that engaged in more mating events were more likely to become infected, whereas mating history had no effect on infection risk when the primary case was female.

DISCUSSION

Individuals' disease risk is likely influenced jointly by individual traits and social contexts, though these 2 factors are rarely tested in unison. Here, we used 3 genotypes of the fruit fly *D. melanogaster* and the generalist fungal entomopathogen *M. robertsii* as a model to test how host genotype, group sex ratio, and the sex of the primary case influence aggregation behavior, mating dynamics, and infection prevalence. We found that fly genotypes vary substantially in their aggregation and mating behavior. However, infection risk was predicated jointly on individual and group factors. We found a greater infection prevalence in female-biased groups, though males experienced 4 times the prevalence of infection compared to females in groups with a female primary case. Further, individuals that mated more were more likely to become infected, but only in the presence of a male primary case. These results indicate the importance of incorporating factors of individual traits and social context into studies of infection risk.

Effects of group sex ratio on behavior and infection risk

Among human and wildlife diseases, infectious disease dynamics vary across social contexts because of differences in the frequency and

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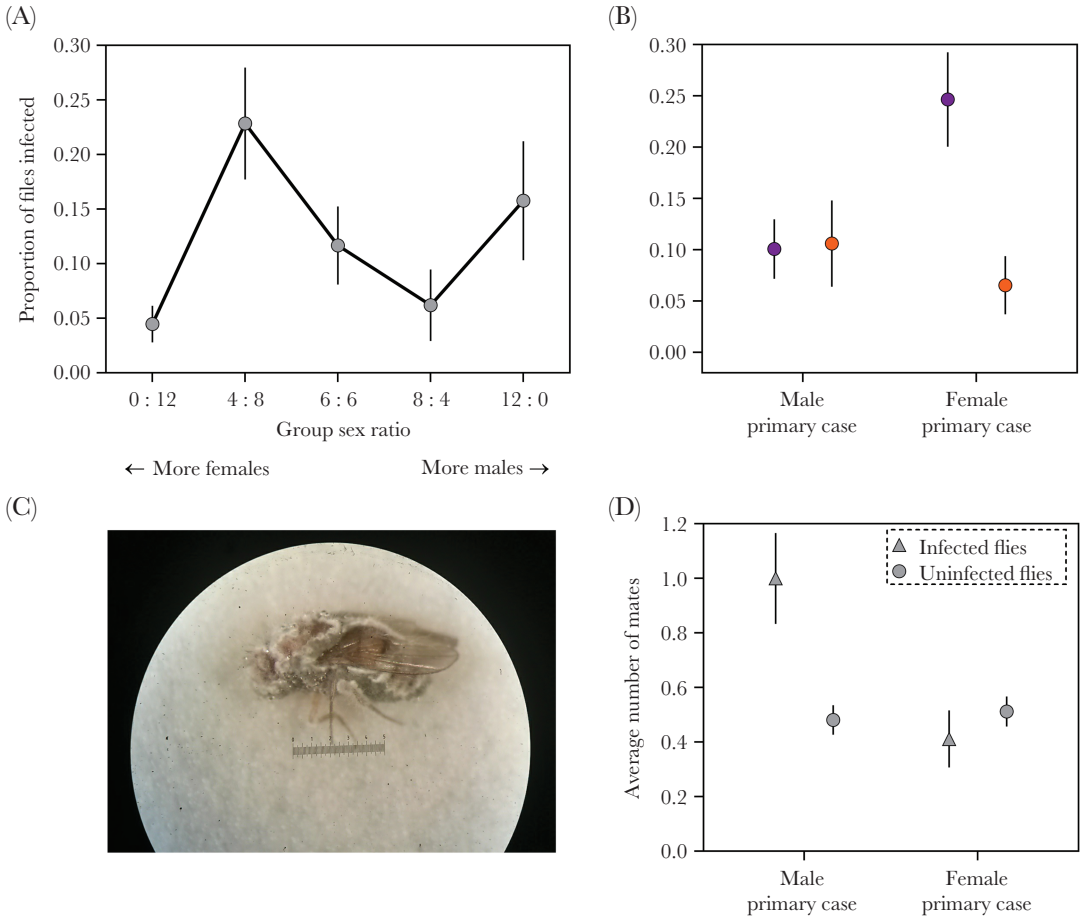

Figure 3

Infection risk across different social contexts. (A) We observed more infections in female-biased groups. (B) When a female primary case was present, males experienced 4 times the prevalence of infection compared to females, but the risk of infection did not differ between males and females when the primary case was male. (C) Example infected fly 48 h after surface sterilization. (D) In the presence of a male primary case, individuals that engaged in more mating were more likely to become infected, whereas mating history had no effect on infection risk in the presence of a female primary case.

nature of contacts between hosts. Specifically, individuals alter their social tendencies and reproductive decision making in response to the sex ratio of their available social partners (Ah-King and Gowaty 2016), which likely has downstream consequences on disease risk. We found that, on average, aggregation increased in groups that were more male-biased. Male *Drosophila* interact aggressively with other males and court potential mates on food patches (Hoffmann 1987), so greater patch-use in male-biased groups is likely a product of males' mate-seeking behavior. The effect of group sex ratio appears to mimic previous studies' effects of group size on aggregation, where individuals are more likely to aggregate in the presence of larger groups (Saltz 2011). However, it is the actions of those individuals during aggregation that will influence infection risk.

Mating frequency was greater in groups that were intermediately female-biased. Previous research has similarly suggested that female-biased sex ratios can alters mating dynamics in *D. melanogaster* (Pavković-Lučić et al. 2009). In many animals, females are unlikely to remate quickly (Gromko et al. 1984; Cook and Wedell 1999; Pitnick et al. 2001; Denis et al. 2017), so female-biased sex ratios allow for more mating events to take place before all receptive females have mated (Alonso-Pimentel and Papaj 1996; Kvarnemo and Ahnesjo 1996; Markow 2002). Thus, it may seem intuitive that more mating events should have occurred in all-female groups with a male primary case because of so many mating opportunities for that infected male. However, female flies often avoid mating with males they just observed copulating (Loyau et al. 2012), so the transmission potential of a single infected male in a group of females may be reduced despite the abundance of potential mating opportunities.

Infection risk was greatest in groups with intermediately female-biased sex ratios, and decreased as groups became more male biased, similar to the trend observed with mating frequencies. Thus, as in many other systems (Altizer et al. 2003), infection risk paralleled one factor of social behavior (mating) more than another (aggregation). We hypothesize that increased infection risk within female-biased groups was a product of increased frequency of reproductive behaviors like courtship and mating. The increased potential for pathogen exposure in groups that engage in more reproductive behaviors may be compounded by individuals' hormonal profiles during courtship, where some reproductive hormones can act as immunosuppressors and potentially increase infection risk (Rantala et al. 2003; Grear et al. 2009; Hawley et al. 2011). However, we also found that 10% of flies that never mated also became infected, so the mode of transmission is not purely sexual. Flies may pick up conidiospores from the substrate (see supplemental materials) or become exposed during courtship, which is sufficient for transmission of pathogenic bacteria in *D. melanogaster* (Miest and Bloch-Qazi 2008).

We found no evidence that the number of mating events differed between social groups with or without an infectious fly present.

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However, we observed 60% fewer flies aggregating on the food patch when there was an infectious fly present compared to control groups. This suggests that flies may be able to discern the infection status of conspecifics and avoid food patches containing infected individuals (Loehle 1995; Kiesecker et al. 1999; Curtis 2014), or perhaps that exposure to pathogens alters flies' space-use patterns or feeding (Ayres and Schneider 2009), thus decreasing overall aggregation. However, individuals may prioritize the opportunity to mate over avoidance of potential infection (Lopes et al. 2013). Future studies should investigate flies' abilities to discern infection risk as a product of their social environment and the role this plays in social group formation.

Effects of the primary case on disease dynamics

We found a 4-fold increase in the risk of males becoming infected when in the presence of a female primary case. Sex-differences in contributions to disease dynamics are common in nature (Zuk and McKean 1996), attributable in part to sexual dimorphism in host phenotypes and susceptibility to infection (Klein 2000; Gipson and Hall 2016). Although there are notable exceptions, many studies find that males are more susceptible to infectious diseases than females (Alexander and Stimson 1988; Bundy 1988; Zuk 2009). Increased male mortality here was context-specific, however, so these patterns are not simply a matter of males being universally more susceptible hosts. For example, in social groups of the European badger, the risk of bovine tuberculosis infection is increased for males that reside in female-biased groups (Vicente et al. 2007). Furthermore, because *D. melanogaster* females are generally larger than males (Partridge and Farquhar 1983), they may harbor more conidiospores on their cuticles, potentially increasing their pathogen shedding rate. On the other hand, in social groups where the primary case was male, flies that mated more often were more likely to become infected. Therefore, the sex of the primary case also appears to have an influence over the degree to which repeated mating predicts infection risk.

Conclusions and future directions

Infection risk is jointly influenced by host traits and the social context in which interactions with infectious individuals may take place. Here, we found that *D. melanogaster* genotypes varied substantially in measures of aggregation behavior and mating dynamics, though we found no evidence for concomitant differences in infection risk. However, a combination of individual-level (individual mating history; the sex of the primary case) and group-level factors (sex ratio) jointly influenced individuals' infection risk. It may also be that an individual's risk of exposure to pathogens via behavioral tendencies (e.g., higher aggregation and mating) may be offset by their immune resistance to infection, as predicted by life history theory (Johnson et al. 2012; Sears et al. 2015). Widescale genotypic differences in *D. melanogaster* resistance to *Metarhizium* infection have recently been demonstrated (Wang et al. 2017), making this a useful model system to test the relative contributions of behavior and immunity on infection risk. More studies in disease ecology should therefore adopt an "interactionist" perspective, accounting for how hosts' traits are expressed across different social contexts to better predict disease outcomes (Eysenck 1991; Capitanio et al. 2008). Our data suggest that an individual's social environment can be an important predictor of both social and sexual dynamics and their survival outcomes.

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Data accessibility Analyses reported in this article can be reproduced using the data provided by Keiser et al. (2018).

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