Article Summary Line: By evaluating disease tolerance as a multifaceted host response, we find that tissue-specific tolerance (milder pathology) impedes transmission while behavioral tolerance (milder anorexia) facilitates transmission of an infectious pathogen.

Running Title: Disease tolerance alters host competence

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Title: Disease tolerance alters host competence in a wild songbird

Authors: Rachel M. Ruden and James S. Adelman

Affiliations:

Iowa State University, Ames, Iowa, U.S.A. (R. Ruden, J. Adelman)

Iowa Department of Natural Resources, Des Moines, IA, U.S.A. (R. Ruden)

University of Memphis, Memphis, TN, U.S.A. (J. Adelman)

Abstract

Individuals can express a range of disease phenotypes during infection, with important implications for epidemics. Tolerance, in particular, is a host response that minimizes the per-pathogen fitness costs of infection. Because tolerant hosts show milder clinical signs and higher survival, despite similar pathogen burdens, their potential for prolonged pathogen shedding may facilitate the spread of pathogens. To test this, we simulated outbreaks of mycoplasmal conjunctivitis in house finches, asking how the speed of transmission varied with tissue-specific and behavioral components of tolerance, milder conjunctivitis and anorexia for a given pathogen load, respectively. Because tissue-specific tolerance hinders pathogen deposition onto bird feeders, important transmission hubs, we predicted it would slow transmission. Because behavioral tolerance should increase interactions with bird feeders, we predicted it would speed transmission. Our findings supported these predictions, suggesting that variation in tolerance could help identify individuals most likely to transmit pathogens.

Introduction

Host competence, or the ability to transmit pathogens, is highly variable across individuals [1-4]. This variation can alter the persistence and magnitude of disease outbreaks [5-7], so understanding its underlying causes is crucial for predicting or mitigating epidemics. One obvious driver of competence is the presence of pathogen, but more subtle aspects of clinical presentation, or disease phenotype, also contribute [8, 9]. For example, tolerance describes a spectrum of disease phenotypes that reduce the per-pathogen costs of infection on host fitness [10]. Originally studied in animals as the population-level slope between pathogen load and pathology [11], with a shallower slope indicating higher tolerance, recent work has focused on tolerance in individuals, using pre- and during-infection data to calculate individual slopes [2-4, 12]. Because tolerant individuals experience fewer deleterious impacts of disease, they may contact more susceptible hosts or fomites while infectious. As such, more tolerant hosts could be more competent [2, 4]. However, because clinical signs often aid transmission (e.g., coughing) and tolerant individuals experience milder disease, these hosts may shed fewer pathogens while infectious [8, 9]. As a result, more tolerant hosts could be less competent [12, 13]. We reconcile these contrasting predictions by deconstructing tolerance into two components and evaluating their effects on transmission.

We break tolerance into tissue-specific and behavioral components by measuring two related responses to infection: pathology and sickness behaviors [12]. Pathology describes the immediate costs of infection due to pathogen-induced tissue damage [14], whereas sickness behaviors, like lethargy and anorexia, capture the opportunity costs of becoming diseased [15, 16]. By reducing the magnitude of pathology at a given pathogen load, tissue-specific tolerance preserves physiological function, and thus host fitness [17]. Similarly, by expressing fewer

sickness behaviors at a given pathogen load, behaviorally tolerant hosts can allocate more time to fitness-enhancing activities like foraging [12]. As they relate to host competence, tissue-specific tolerance can alter pathogen shedding from infected tissues, while behavioral tolerance can impact contact rates among individuals.

We explore how tissue-specific and behavioral tolerance alter host competence using a model infectious disease system, house finches (*Haemorhous mexicanus*) infected with *Mycoplasma gallisepticum* (MG). This bacterial pathogen first emerged in songbirds in the early 1990s, presenting as conjunctivitis [18]. Bird feeders serve as critical transmission hubs in this system, congregating individuals and acting as fomites [19, 20].

Although both resistance (clearing pathogens) and tolerance vary across house finch populations [21-23], tolerance may be particularly helpful in predicting competence. Specifically, we expect tissue-specific tolerance (milder conjunctival pathology for a given pathogen load) to reduce transmission speed because 1) even when controlling for pathogen load, pathology increases pathogen deposition onto bird feeders [24], 2) the amount of pathogen a naïve bird encounters (infectious dose) predicts its probability of infection [25], and 3) pathology increases transmission speed across MG isolates [8, 9]. Notably, this finding across isolates does not exclude pathogen load as a potential driver of competence across individual hosts. Rather, it supports incorporating both pathogen load and pathology (e.g., tissue-specific tolerance) when studying finch competence. In contrast to tissue-specific tolerance, we expect behavioral tolerance (milder anorexia for a given pathogen load) to increase transmission speed because infected finches that spend more time on bird feeders are more likely to transmit [20]. We evaluated these predictions using co-housed pairs of finches, experimentally inoculating one

bird, calculating its tissue-specific and behavioral tolerance, then measuring time until transmission to its cage-mate.

Methods

Capture Sites and Initial Housing

We captured house finches using mist nets between 6 July and 17 September, 2017 in Ames, Iowa, USA. We aged birds via plumage and retained hatch-year individuals [26], which are at lowest risk for prior pathogen exposure. After arriving at Iowa State University, birds were housed individually for a minimum 14d quarantine, as in prior studies (see Supplemental Material). ~~After quarantine, 22 of the~~Twenty-two birds utilized in the experiment~~s~~ below were then housed in mixed-sex~~randomly-assigned~~ 'flocks' of three for a separate experiment (see Supplemental Material)~~, two were housed individually. We~~ and videoed ~~each flock~~ (Action Cameras, YI Technology, Bellevue, WA), using one-hour focal surveys to rank individuals by feeding frequency. An additional two birds were housed individually as sentinels.

Pair-housed transmission experiment

After the ~~aforementioned~~ flock study, twenty-four birds (14 female, 10 male) showed no clinical or serological signs of MG infection and were moved into pairs at different times, as verification of disease status allowed. Seven pairs were established from existing flocks immediately (25d pre-inoculation; 3 female-female and 4 mixed-sex pairs); two ~~five~~ mixed-sex pairs were co-housed between 24 and 17d pre-inoculation (2 mixed-sex pairs); and three pairs were formed 7d pre-inoculation (1 male-male and 2 mixed-sex pairs).~~If two birds from the same flock showed no signs of MG exposure, they were retained as a pair (n=14); if only one bird from a flock showed no such signs, it was randomly assigned a partner with whom it had not previously been housed (n=10).~~ Cages (76 x 46 x 46 cm) sat on individual racks with plastic

curtains on either side to reduce chances of cross-cage exposure. To minimize transmission variation due to baseline feeding propensity [20], we selected the bird that fed more often for experimental MG-inoculation ("inoculated" bird). For pairs that were housed together previously, we used feeding ranks from the above study; for those not previously housed together, we recorded new one-hour videos.

Prior pilot work suggested that meloxicam, a non-steroidal anti-inflammatory drug, enhanced tissue-specific tolerance, i.e., reduced conjunctivitis without changing pathogen load (RMR, unpublished data). We therefore attempted to enhance tissue-specific tolerance in half of the inoculated birds by treating with 2µL/g body mass/day oral meloxicam (0.5µg/µL), while other inoculated birds received 2µL/g/day oral water, from 2d pre-inoculation through 21d post-inoculation. Both treatments were chased with 100µL water to encourage swallowing. Treatment showed no effect on transmission (see Results).

On 11 December, 2017 (day 0), one bird per pair (7 female, 5 male) was inoculated with MG (stock 2006.080-5(4P) 7/26/12, David Ley, North Carolina State University). We applied 25µL of Frey's medium containing 6.25 x 10^4 color-changing units of MG to each eye via micropipette, with birds maintained in horizontal recumbency until fluid dissipated beneath the eye rim.

To assess feeding behavior, we videoed pairs weekly for one-hour beginning five minutes after lights-on (0600h). For each video, we completed two 10s scan samples every minute, during which birds were assigned a "1" if they fed and a "0" if they did not. Due to limited cameras, we typically split recording across sequential days~~: 11-12d pre-inoculation and 3-4, 10-11, 17-18 and 32-33d post-inoculation~~. We recorded the nine earliest-formed pairs 11-12d pre-

inoculation and the three later-formed pairs 1d pre-inoculation, all at least 5d after co-housing. All pairs were recorded 3-4, 10-11, 17-18, and 32-33d post-inoculation. We sampled more intensely early in infection because prior experiments found the majority of transmission within 20d post-inoculation [9, 20].

We scored conjunctivitis on a four-point scale from 0 (no pathology) to 3 (severe pathology) per eye [27], summing these for a total eye score. We monitored pathogen load by abducting the lower eye rim with sterile forceps, inserting a sterile cotton swab dipped in tryptose phosphate broth (TPB), and rotating for 5s. For each bird, swabs from both eyes were rung out into one microcentrifuge tube containing 300 µL TPB and stored at -20°C until DNA extraction (DNEasy Blood and Tissue kit, Cat no. 69504/69506, Qiagen, Valencia, CA). We measured pathogen load as the number of copies of the *mgc2* gene, of which each bacterial cell has one copy, via quantitative polymerase chain reaction using previously described conditions and primers [28]. Birds were eye-scored 3x per week for three weeks, then 2x per week afterward. Swabs were collected from non-inoculated birds 2x per week for three weeks, then 1x per week afterward, and from inoculated birds 1x per week throughout. All inoculated birds became infected (maximum $\log_{10}$(load) within individual: mean = 6.18, SD = 0.84, range = 3.65–6.85; maximum eye score within individual: mean = 4.33, SD = 1.49, range = 1–6, Figure S1).

Quantifying tolerance

We calculated inoculated birds' tolerance using two data points per individual, one pre-infection and another during a transmission window specific to each pair—between inoculation and the day pathology was first detected in the cage-mate. If the cage-mate showed no pathology, the window ended on the study's final day (43d post-inoculation).

For each individual, i, we defined tissue-specific tolerance as

$$-\left(\frac{maximum\ eye\ score_{i,transmission\ window} - eye\ score_{i,initial}}{maximum\ pathogen\ load_{i,transmission\ window} - pathogen\ load_{i,initial}}\right) \quad \text{Eq. 1}$$

and behavioral tolerance as

$$\frac{lowest\ feeding\ frequency_{i,transmission\ window} - feeding\ frequency_{i,initial}}{maximum\ pathogen\ load_{i,transmission\ window} - pathogen\ load_{i,initial}} \quad \text{Eq. 2}$$

We use a negative in Eq. 1, but not Eq. 2 so negative values indicate lower tolerance in both cases, simplifying interpretation. This was done because pathology increases during infection, but feeding often decreases (Figure S2).

Among inoculated birds, pre-infection pathogen load was either undetectable (6/12) or <16 copies of the *mgc2* gene, excepting one individual (134 copies, or < 1/10,000th the average pathogen load of >10^6 during peak infection), consistent with negligible prior exposure or environmental contamination. Excluding that individual yielded qualitatively identical results (see Supplemental Materials). Among non-inoculated birds, pre-infection pathogen load was either undetectable (8/12) or <11 copies, excepting one individual (31 copies). Tissue-specific and behavioral tolerance showed no correlation (Pearson's r = -0.08, t10 = -0.26, p = 0.80; Figure S1).

Statistical analysis

We tested how time to transmission varied with tissue-specific and behavioral tolerance using accelerated failure time models in the 'survival' package [29, 30] in R [31]. Such models estimate the time to an event (e.g., transmission, death) from datasets in which the event does not necessarily occur in all cases. First, we fit a maximal model with either Weibull, logistic,

lognormal, loglogistic, or exponential errors, selecting loglogistic via Akaike's Information Criterion for small sample sizes (AICc) [32]. This model included five predictors: tissue-specific and behavioral tolerance, maximum pathogen load during the previous flock study for both inoculated and non-inoculated birds (see Supplemental Material), and NSAID treatment of the inoculated bird. Continuous predictors were standardized to z-scores by taking the difference between an individual observation and the sample mean, then dividing that difference by the sample standard deviation. To avoid over-parameterization, we selected the best-fit of 26 simplified models, including an intercept-only model, each with a maximum of three predictors (Table S1). We also calculated each predictor's relative importance [32].

Results

The best-fit model of time to transmission contained three predictors: tissue-specific tolerance, behavioral tolerance, and maximum pathogen load in the inoculated bird during the prior study. Two other models showed ΔAICc < 2 and contained tolerance variables (Table 1). Tissue-specific tolerance showed the highest relative importance (0.98), followed by behavioral tolerance (0.62) and maximum pathogen load in the inoculated birds during the prior study (0.55). Meloxicam treatment status did not appear in any models with ΔAICc < 6.

Based on the best-fit model, for every unit increase in tissue-specific tolerance (milder conjunctival pathology), birds transmitted ~1.8 times more slowly (estimate = 0.57, z = 4.77, $p <$ 0.01; Figure 1A). In contrast, for every unit increase in behavioral tolerance (milder anorexia), birds transmitted ~1.7 times more rapidly (estimate = -0.55, z = -2.97, $p < 0.01$; Figure 1B). For each unit increase in maximum MG load in the prior study, birds transmitted ~1.4 times more

rapidly, although this effect appeared driven by one bird (estimate = -0.33, z = -4.32, $p < 0.01$; Figure S2).

Discussion

We evaluated how tissue-specific and behavioral components of disease tolerance altered host competence in house finches, measured as time to MG transmission. Consistent with our predictions, birds with higher tissue-specific tolerance were less competent (transmitted more slowly), whereas those with higher behavioral tolerance were more competent (transmitted more rapidly). These results complement the recent finding that MG isolates inducing greater pathology transmit more rapidly [9]. Specifically, we tested inter-host variation, rather than inter-isolate variation, finding that sickness behaviors may offset transmission-enhancing effects of pathology.

This negative relationship between tissue-specific tolerance and competence is expected when pathology enhances transmission, as in finch MG and numerous other systems [12, 13]. For example, larvae of the trematode *Ribeiroia ondatrae* encyst in the limb buds of tadpoles, resulting in a range of pathologies at metamorphosis that facilitate predation by definitive hosts [33]. But, species that metamorphose later and at larger body sizes show higher tissue-specific tolerance, measured as fewer limb abnormalities for a given parasite load [33]. Such animals should be more adept at escaping predators, meaning tissue-specific tolerance would also reduce competence in that system.

Additionally, the positive relationship between behavioral tolerance and competence is expected when sickness behaviors reduce contact rates [15, 16], thereby impeding transmission. Behavioral tolerance may similarly impact competence in other disease systems, although

specific details will differ. For example, bat mortality from White-Nose Syndrome stems in part from increased arousals during torpor, which burn through hosts' energy reserves [34]. Notably, big brown bats (*Eptesicus fuscus*) likely show higher behavioral tolerance, expressing longer bouts of torpor, than little brown bats (*Myotis lucifugus*) [35]. This higher behavioral tolerance (prolonged torpor) may allow the slow-growing, psychrophilic fungus to infect more neighbors at a roost site, facilitating competence.

In addition to the above tolerance metrics, our best-fit model included prior pathogen load in the inoculated bird. However, this variable explained less of the variation in time to transmission than did either tolerance metric, with a smaller absolute value for its parameter estimate and lower relative importance. Additionally, the relationship between prior pathogen exposure and time to transmission was driven by one bird (Figure S2), suggesting a spurious correlation. That individual's pathogen load during the current study was typical for naïve house finches [23], suggesting its prior exposure did not impact its current disease course: it showed fewer than 10 copies of MG at the start of this study and $>10^6$ copies three days after inoculation. Thus, in this study, tolerance metrics remain more likely drivers of host competence than does prior exposure.

Although pathology has been the primary proxy for fitness in studies of disease tolerance in animals [10], we found that a more nuanced evaluation of tolerance better informs transmission dynamics. Specifically, we found opposing effects of tissue-specific and behavioral tolerance on host competence in this system, whereby hosts showing higher behavioral and lower tissue-specific tolerance should be most competent (Figure 1, Video S1). However, the contribution of each tolerance component likely varies across pathogen types, transmission modes, and tissue tropisms [12, 13]. In the future, capturing more subtle variations in pathology

(beyond relative severity) may help identify links between tissue-specific tolerance and transmission [36]. Likewise, additional metrics of sickness behavior, like changes in sociality, may refine estimates of how behavioral tolerance alters transmission. Regardless, our results suggest that measuring tissue-specific and behavioral components of tolerance can help us understand its impacts on host competence and epidemic outcomes.

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Tables and Figures Captions

Table 1. Best supported accelerated failure time models of time to *Mycoplasma gallisepticum* transmission in 12 pairs of captive house finches.

Model	Predictor(s)	AICc	ΔAICc	Weight
1	Tissue-specific Tolerance, Behavioral Tolerance, Inoculated Bird Maximum Pathogen Load (Prior Study)	63.14	0.00	0.36
2	Tissue-specific Tolerance, Behavioral Tolerance	64.09	0.96	0.22
3	Tissue-specific Tolerance	64.91	1.78	0.15
4	Tissue-specific Tolerance, Inoculated Bird Maximum Pathogen Load (Prior Study)	65.53	2.40	0.11
5	Tissue-specific Tolerance, Inoculated Bird Maximum Pathogen Load (Prior Study), Naïve Bird Maximum Pathogen Load (Prior Study)	66.68	3.55	0.06

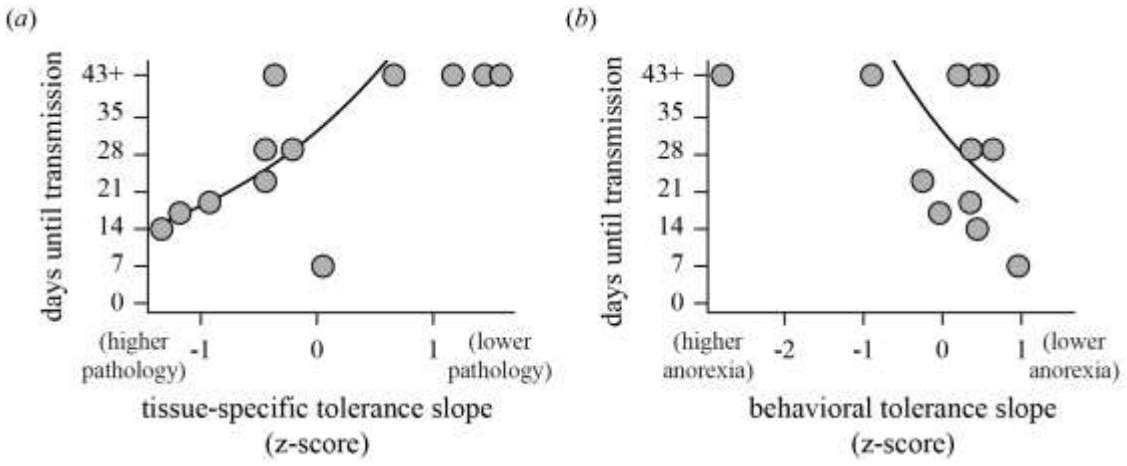

Figure 1. House finches with higher tissue-specific tolerance (milder conjunctivitis) transmitted *Mycoplasma gallisepticum* more slowly (*a*); those with higher behavioral tolerance (milder anorexia) transmitted more rapidly (*b*). Lines show predictions from the top accelerated failure time model with other variables held at their means.