Dynamics of a novel pathogen in an avian host: Mycoplasmal conjunctivitis in house finches

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Abstract

In early 1994, a novel strain of *Mycoplasma gallisepticum* (MG)—a poultry pathogen with a world-wide distribution—emerged in wild house finches and within 3 years had reached epidemic proportions across their eastern North American range. The ensuing epizootic resulted in a rapid decline of the host population coupled with considerable seasonal fluctuations in prevalence. To understand the dynamics of this disease system, a multi-disciplinary team composed of biologists, veterinarians, microbiologists and mathematical modelers set forth to determine factors driving and influenced by this host–pathogen system. On a broad geographic scale, volunteer observers ("citizen scientists") collected and reported data used for calculating both host abundance and disease prevalence. The scale at which this monitoring initiative was conducted is unprecedented and it has been an invaluable source of data for researchers at the Cornell Laboratory of Ornithology to track the spread and magnitude of disease both spatially and temporally. At a finer scale, localized and intensive field studies provided data used to quantify the effects of disease on host demographic parameters via capture–mark–recapture modeling, effects of host behavior on disease and vice-versa, and the biological and genetic profiles of birds with known phenotypic characteristics. To balance the field-based component of the study, experiments were conducted with finches held in captivity to describe and quantify the effects of experimental infections on hosts

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in both individual and social settings. The confluence of these various elements of the investigation provided the foundation for construction of a general compartmentalized epidemiological model of the dynamics of the house finch–MG system. This paper serves several purposes including (i) a basic review of the pathogen, host, and epidemic cycle; (ii) an explanation of our research strategy; (iii) a basic review of results from the diverse multi-disciplinary approaches employed; and (iv) pertinent questions relevant to this and other wildlife disease studies that require further investigation.

1. Introduction

In recent years, emerging infectious diseases (EIDs) have posed increasing threats to wildlife and human health. The vast majority of disease emergence events have been driven by human activities (Daszak et al., 2000), and mechanisms of emergence fall into three broad categories: (1) new infections caused by pathogen spill-over from domestic to wild animals, (2) novel introductions resulting from human translocation of hosts or pathogens, or (3) environmental changes driven by pollution and habitat destruction that allow existing pathogens to increase in prevalence or severity through altered host susceptibility or rates of disease transmission. Although the initial cause of any particular EID may be easy to ascertain, it is more difficult to describe the resulting ecological and evolutionary interactions between a pathogen and its novel hosts, and to assess the effects of emerging diseases on wild host populations.

Despite the paucity of knowledge of EIDs in wildlife, the recent occurrence of a novel strain of the pathogen *Mycoplasma gallisepticum* (MG) in wild house finches (*Carpodacus mexicanus*) has provided a unique opportunity to investigate host–pathogen dynamics in the wild from its outset. This novel strain of MG first emerged in house finches in the winter of 1993–94 and within a few years had spread throughout the house finches' introduced eastern range (Ley et al., 1996; Fischer et al.,1997; Ley et al., 1997). The bacterium has now reached the western, native range of the house finch (Duckworth et al., 2003) and poses the threat of a new epidemic. In eastern North America it continues to persist and undergoes highly seasonal epidemics (Hartup et al., 2001a; Altizer et al., 2004b).

The origin of this bacterial pathogen most likely falls into group (1) above, because MG is a world-wide pathogen of commercial and non-commercial (e.g. 'backyard') domestic poultry (primarily chickens and turkeys), and because house finches, as seed eaters, associate frequently with poultry farms and perhaps more importantly backyard poultry flocks (Luttrell et al., 2001), which may have a much higher prevalence of MG (Ewing et al., 1996; McBride et al., 1991) and little or no biosecurity. However, the presence of the house finch in eastern North America is also the result of an artificial introduction, so that the host–pathogen system could also be placed in group (2).

Many features of the *M. gallisepticum*–house finch system have allowed a unique examination of host–disease interactions at many different levels simultaneously. The long history of monitoring house finch populations prior to the emergence of MG as a pathogen (via the Christmas Bird Count and the Breeding Bird Survey) has given us a broad-scale background against which to assess the impacts of the disease. The highly visible outward signs of the disease (severe conjunctivitis; Hartup et al., 1998), coupled with close association of house finches with humans have allowed the documentation of spread and persistence of the disease in the wild. The predisposition of house finches to associate with humans has also allowed intensive study of individual wild birds and their responses to MG. Wild house finches are easy to capture and maintain in captivity, facilitating examination of physiological responses of finches to MG infection, observations of behavioral changes following infection and studies of factors affecting susceptibility, transmission and recovery.

We introduce this study system and set the stage for our goals and findings by first reviewing the key characteristics of the pathogen, the host, and the history behind this emerging disease. Then we will describe the multiple approaches used simultaneously to investigate this system, and highlight recent results that have both deepened our understanding of wildlife–pathogen

interactions and raised new and exciting questions for further research.

2. *M. gallisepticum*: the pathogen

M. gallisepticum (MG) is a bacterium of the class Mollicutes and family Mycoplasmataceae (Ley, 2003). Mycoplasmas lack a cell wall and are the smallest self-replicating prokaryotes (Razin, 1995). MG is one of 23 *Mycoplasma* species that have been recovered from avian sources, and one of three pathogenic species common in domestic poultry (Jordan, 1996). In domestic poultry, MG is frequently associated with respiratory tract disease, debilitation, carcass condemnation and reduced egg production in chickens and turkeys (Mohammed et al., 1987; Jordan, 1996; Ley, 2003). Recent experimental trials have shown that chickens exposed to the house finch strain of MG seroconvert and may develop mild disease (Stallknecht et al., 1998; O'Connor et al., 1999).

Historically, MG has not been considered a naturally occurring pathogen in wild birds. Although isolations have been documented in several bird species, sustained reservoirs in wild birds have not been previously identified (Jain et al., 1971; Shimizu et al., 1979; Reece et al., 1986; Poveda et al., 1990; Fritz et al., 1992; Cookson and Shivaprasad, 1994). Furthermore, MG infections in free-ranging birds other than house finches appear infrequently (Hartup et al., 2000; Hartup et al., 2001b; Mikaelian et al., 2001), and host specificity is considered a hallmark of the mollicute–host relationship (Tully, 1996) —supporting observations that this emergence event was largely limited to house finches, at least initially.

How did MG enter wild house finches, and from what source? Existing evidence points to a single emergence event in the Washington, DC area. Thus, Ley et al. (1997) found that random amplification of polymorphic DNA (RAPD) genotype patterns from MG isolates collected from wild house finches in 11 Eastern and Midwestern states from 1994–96 were nearly identical to each other, but notably different from multiple laboratory reference strains, vaccine strains, and poultry field isolates. The result was interpreted as suggesting a single source for the epidemic, confirming the singularity of the finch MG strain among songbirds through the initial phase of the epidemic. Recent sequence analysis

of *pvpA* gene PCR products showed that although most house finch MG isolates clustered more closely to each other, others clustered more closely to either turkey or chicken field isolates. This finding suggests that house finch isolates are more polymorphic than previously recognized by RAPD-based studies (Pillai et al., 2003).

MG is thought to be transmitted primarily through direct contact between infected and susceptible individuals (Ley, 2003). However, contact with contaminated surfaces, airborne droplets, dust or feathers can also result in disease spread (Christensen et al., 1994; Gerlach, 1994). In domestic poultry, vertical transmission through the egg has been well documented and is an important factor in the epidemiology of disease, but often occurs sporadically and at low prevalence (Calnek and Levine, 1957; Fabricant et al., 1959; Kempf and Gesbert, 1998). In wild house finches, Hartup and Kollias (1999) documented MG infections in broods of house finch chicks but failed to document egg transmission of MG in house finches, which suggested the possibility of pseudovertical transmission between parents and dependent young. Using polymerase chain reaction (PCR), MG infection was confirmed in 1 of 42 eggs in a captive aviary flock, thus documenting one case of vertical transmission, although the viability of the MG detected was not determined (Sydenstricker and Ley, unpublished). More observations and experiments are needed to determine if vertical transmission could contribute to the persistence of MG in house finch populations. Future directions also include quantifying horizontal transmission probabilities resulting from contact with infected birds and contaminated surfaces.

3. *C. mexicanus*: the host

The house finch *C. mexicanus* is a small (20 g) passerine bird that originally inhabited arid lands up to 2000 m in western North America. The species prefers edge habitat, but is also found in association with human habitation in the west. Recent expansion of the native population has occurred following urbanization of western landscapes (Hill, 1993).

The species was successfully introduced into Hawaii around 1870, and pet birds were later released in Long Island, New York in 1940. On Long Island, the introduced population barely survived the cold winter

of 1947–48, when the population numbered "several dozen" individuals (Elliott and Arbib, 1953). Beginning around 1960 the eastern population began to expand rapidly in size and geographic range (Hill, 1993). It has gradually developed migratory behavior and is now partially migratory, with a proportion of the population flying to wintering sites from November through February (Belthoff and Gauthreaux, 1991; Able and Belthoff, 1998). Although the introduced eastern and the native western populations have now joined, house finch abundance was until recently, still rapidly increasing at the periphery of its eastern range (Hochachka and Dhondt, 2000).

In the east, house finches are most commonly found in association with humans. They prefer areas with buildings, lawns and small conifers, but are also found in urban centers. House finches feed opportunistically on seeds, and therefore often visit bird feeders (e.g. 73% of all observers in the Cornell Laboratory of Ornithology's Project FeederWatch report visits by house finches). House finches are non-territorial and can breed alone or in loose colonies. They have an extended breeding season, and females can lay multiple clutches between March and July (Hill, 1993). Outside the breeding season the species is highly gregarious, and is often found in and around buildings and food sources, including commercial poultry facilities. The non-breeding ecology and behavior of house finches is not well studied, although a quantitative understanding of social organization and mobility is essential to understand the spread and dynamics of disease. House finches roost socially, often in association with ornamental spruce trees, but roost ecology is not well understood (see Swarthout et al., unpublished manuscript).

4. Emergence of a new disease

The first reports of multiple house finches with diseased eyes occurred in early 1994 in the Maryland suburbs northwest of Washington, DC. This novel disease spread rapidly, and by October 1994 house finches with severe conjunctivitis were being reported across several U.S. states between North Carolina and New York (Fischer et al., 1997; Fig. 1). The pathogen causing this new disease in house finches was identified as a previously unknown strain of *M. gallisepticum* (Ley et al., 1996; Luttrell et al., 1996).
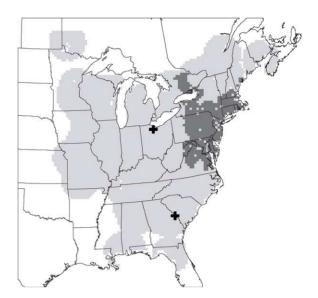

Fig. 1. Distribution of mycoplasmal conjunctivitis in November 1994, the first month in which the HFDS reported data. Dark gray denotes areas where both house finches and conjunctivitis were observed, and light gray shows areas where house finches occurred without conjunctivitis. Note two isolated cases of conjunctivitis in South Carolina and in Ohio indicated by crosses (after Dhondt et al., 1998).

Within months of its emergence Dhondt et al. (1998) began a systematic survey of the prevalence of conjunctivitis in eastern North America. The "House Finch Disease Survey" (HFDS), which began in November 1994, provides a means of tracking MG spread and disease frequency from systematic reports provided by large numbers of "citizen scientists" across North America (Fig. 1). Because the physical signs of infection are visually obvious (swollen conjunctival tissue, crusty or serous secretions) and can be seen from a distance, and because house finches, especially in the eastern part of their range commonly visit feeders, it was possible to involve the thousands of volunteer-observers who feed and watch birds in their yards and who already participated in the Cornell Lab of Ornithology's Project FeederWatch (Dhondt et al., 2001).

The initial goal of the HFDS was to track the spread of the epidemic. We wanted to know when the disease reached a given region, and whether it increased in prevalence following arrival. For that reason we did not ask participants to count numbers of house finches, instead we requested they report the days in which they watched feeders, and whether or not symptomatic
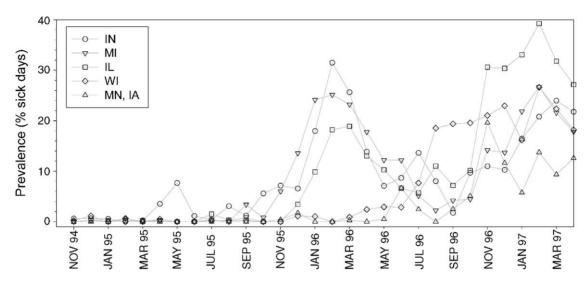
Fig. 2. Onset of mycoplasmal conjunctivitis in some Midwestern states in which the HFDS began before MG reached the area. Prevalence is expressed as percent sick days, which is (the total number of days in a month on which a participant observed at least one house finch with conjunctivitis) divided by (the total number of days on which a participant observed at least one house finch) summed over all participants in a state reporting during a month. Note how the epidemic began in the fall of 1995 in Indiana, Michigan and Illinois, and began in late summer/fall of 1996 in Wisconsin, Minnesota and Iowa. Note also that the strong seasonal fluctuation in prevalence was already observed in the first summer following the arrival of MG.

and/or asymptomatic house finches were observed. Since conjunctivitis can have many causes (such as mechanical irritation, infection by another pathogen), and since we did not know if the epidemic would spread to other wild avian hosts, we requested reports on other bird species as well—including purple finches (*Carpodacus purpureus*), house sparrows (*Passer domesticus*) and black-capped (*Poecile atricapillus*) and Carolina chickadees (*P. carolinensis*). Because we designed and executed the HFDS very quickly, we began collecting data in many parts of North America before the arrival of the pathogen (Fig. 2), thereby making it possible to document in detail the arrival and epidemic expansion in many parts of the host range.

5. Research strategy

Thanks to National Science Foundation funding through the multi-agency "Ecology of Infectious Diseases" program we brought together in September 2000 a multi-disciplinary, multi-institutional team to implement a many-facetted research project.

For results of a study to be of general applicability, they must be placed within a broad conceptual framework. For that reason we viewed the construction,

analysis and refinement of general mathematical models as an essential goal of our work. The process of generating these models has been iterative, with initial models guiding our choice of research topics, and results from the field and aviary research feeding back into the modeling process throughout the course of the study. Such iterative work has required close cooperation between investigators with very different skills and research perspectives.

Our research goals and implementation have been compartmentalized into a series of distinct task-oriented components, with each component the primary responsibility of a different member of the research team. Many members of this team expanded the work scope by involving graduate and undergraduate students to tackle specific components of the project. These components include:

(1) Develop valid mathematical models, which successfully represent the dynamics of the disease, both temporally, and spatially (Dobson, Princeton).
(2) Surveys covering North America to monitor changes in disease prevalence and host abundance over space and time (Dhondt, Cornell).

(3) Combining these results with other continent-wide studies of bird abundance (Breeding Bird Survey, Christmas Bird Count, Project FeederWatch) to determine interactive effects of disease on abundance and social behavior (Hochachka, Cornell).

(4) Intensive field studies in three geographically distinct sites to generate detailed MG prevalence and disease data, and information about host ecology (including survival rates and individual disease risk) and behavior (including feeding behavior, movements and social organization) (Dhondt, Ithaca, NY; Hartup, Madison,WI; and later Altizer, Atlanta, GA). Collaboration with several banders in West Virginia and New Jersey further increased the geographic scope of our intensive local studies.

(5) Use of radio tracking to study house finch movements, social organization and roosting behavior (Dhondt, Cornell).

(6) The development and use of appropriate capture–mark–recapture (CMR) models to examine disease-dependent variation in survival rates, encounter rates, movement rates, and transition rates between asymptomatic and symptomatic observable health states (Cooch, Cornell).

(7) Captive studies to describe the course of disease in infected individuals in controlled conditions, individual responses to re-infection, study experimentally the causes of variation in disease transmission and recovery in groups, and determine experimentally modes of MG transmission (Kollias, Cornell; Ley, NCSU).

(8) Laboratory analyses to confirm the presence of MG in samples using PCR and culture techniques (Ley, NCSU).

(9) Studies of presence of other pathogens or parasites in house finches that could potentially interact with MG infections (Hartup, Madison, WI; Kollias, Cornell).

Although the mathematical models are viewed as laying the groundwork and motivation for components 2 through 9, these models rely heavily on biological patterns and parameter estimates uncovered by analysis of field and experimental data. Thus, in highlighting our approaches and results below, we focus initially on empirical studies, which were motivated by the development of an SIR (susceptible–infected–recovered) model (Anderson and May, 1979). Later, we weave results from each of the empirical components together in describing the construction of and results from subsequently produced comprehensive mathematical models.

6. Progress

6.1. Large-scale studies of prevalence

After launching the HFDS in November 1994, less than a year after the epidemic began, we described the monthly spread of the epidemic during its early stages (see Dhondt et al., 1998) thanks to the thousands of "citizen scientists" who reported observations of asymptomatic and symptomatic house finches (and other birds species) at their bird feeders. By June 2004, we had amassed over 89,575 monthly reports from 10,338 participants. To our amazement, 133 citizen scientists had submitted data for 50 months or more during the past 10 years, and 10 for more than 100 months!

Results from this survey documented the pattern of geographic expansion whereby the disease first spread North, as infected house finches migrated back from their wintering to their breeding grounds, and later South and West (e.g. Figs. 1 and 2). By March 1995, the epidemic, which began in February 1994, covered an area between NH, VT, NY and ON in the north, VA, WV and KY in the south and OH in the west, with a flurry of cases in GA and a few in NC. Because the HFDS began before the epidemic started in the Midwest, we were able to describe in detail its westward spread. In the fall of 1995, the epidemic had reached IN, MI and IL, and in the fall of 1996 it had spread to WI, MN and IA (Fig. 2).

Furthermore, our continued intensive effort to describe disease prevalence demonstrated that once the disease became established, prevalence showed strong seasonal variation (Fig. 4). On average throughout the house finches' eastern range, prevalence bottomed out during the breeding-season and increased to a peak in October or November. A midwinter trough was followed by a second increase during the late-winter or early spring, before returning to the breeding season minimum. Beyond seasonal changes, the large geographic coverage of the HFDS made it possible to detect important geographic differences in seasonal variation. In the South-east (Arkansas, Tennessee,

North Carolina and further south), fall prevalence peaked earlier, and reached a higher maximum prevalence, relative to areas further North (Altizer et al., 2004b). Finally, removal of seasonal trends from annual prevalence changes revealed longer-term fluctuations in prevalence, with multiyear peaks separated by 2–3-year intervals—although in-depth analysis of the regularity of these cycles and potential causes will require additional time series data (Altizer et al., 2004b).

Although we used the Lab of Ornithology's quarterly newsletter Birdscope to regularly report results to participants of this and other Lab of Ornithology projects and to Lab members (40,000 copies), the number of participants gradually decreased between 1997 and 2000. Thanks to the NSF-funding we increased participation substantially via redoubled media coverage and by more closely integrating the HFDS with another Lab of Ornithology project, Project FeederWatch, for those participants who entered data over the internet. The number of participants in the HFDS increased substantially from 2000 onwards, also in the west (Fig. 3). Recruiting and retaining large numbers of participants has been crucial in our efforts to describe geographic and seasonal variation in prevalence (Altizer et al., 2004b; Fig. 4), and to monitor the timing of a potential MG epidemic among house finches in their native western range along with concomitant changes in abundance.

After MG became established in the east, it took another 6 years before the pathogen reached a native western population of house finches in Montana in April 2002 (Duckworth et al., 2003). A general epidemic was not observed in the West at that time. More recently, HFDS observations suggest that an epidemic started in the North-west in January 2004, exactly 10 years after
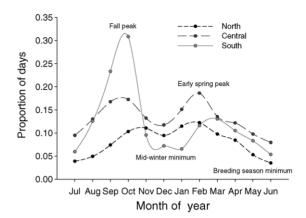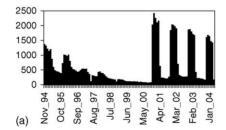

Fig. 4. Seasonal and geographic variation in prevalence of mycoplasmal conjunctivitis in eastern North America. In the South (minimum January temperatures $>-2.9\,°C$: North Carolina, Tennessee, Arkansas and further south) fall peaks are higher and earlier, and spring peaks are later. In the central region (minimum January temperatures are between -3 and $-8.9\,°C$: Virginia, New Jersey, Delaware and Maryland) prevalence peaks and timing are intermediate. In the northern region (minimum January temperatures are $<-9\,°C$: northern parts of Missouri, Illinois, Indiana, Ohio and most of New York, Massachusetts, Vermont, New Hampshire and areas further north) prevalence increases late in the fall and peaks are minimal relative to areas further south (after Altizer et al., 2004b).

the onset of the epidemic in the East (Dhondt et al., unpublished).

6.2. Combining multiple citizen science projects to determine pathogen impacts on house finch abundance and social organization

To determine if an emerging disease impacts host abundance and social organization it is necessary to have data before the disease emerges. In North America, various continent-wide bird-monitoring schemes
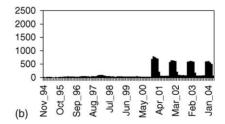

Fig. 3. Monthly number of participants in the House Finch Disease Survey from November 1994 to April 2004 in (a) the eastern United States and Canada and (b) the western United States and Canada. Periodic peaks are due to winter activity of Project FeederWatch participants.

existed prior to MG eruption in finches, providing information on abundance. Since 1900, the Christmas Bird Count (CBC) provides a single count of winter abundance; since 1966 the Breeding Bird Survey (BBS) provides a single count of abundance during the breeding season; and since 1987 Project FeederWatch (PFW) contributes information on the number of birds visiting bird feeders during a 20-week period in winter. All monitoring schemes, therefore, were well underway when in 1994 mycoplasmal conjunctivitis emerged in house finches.

Because in many areas house finch abundance was still increasing, we needed to calculate expected abundance (by fitting Richard growth curves through time-series data) to measure the impact of the disease on host abundance. By combining the CBC with the HFDS we showed that 2.5 years after the MG epidemic hit a region, expected house finch abundance decreased by about 60%, and this effect of MG on house finch abundance was density dependent (Hochachka and Dhondt, 2000) (Fig. 7a).

Furthermore, by combining the HFDS with PFW, we showed that this large-scale decrease in abundance did not cause the geographic distribution of the species to shrink, but caused a decrease in group size at all sites. This decrease in group size was unequal in space. Before the disease arrived in the North-east, groups were larger in the South (Pennsylvania) than in the North (Ontario, Maine). A few years after MG arrived, group sizes became equal everywhere. Similarly, within the North-east U.S. house finch groups were initially larger in rural than in urban areas, but again this difference disappeared after MG became established (Fig. 5). All of these results combined strongly indicate a density dependent regulation of house finch populations by MG in the East (Hochachka and Dhondt, 2000; Hochachka and Dhondt, unpublished manuscript).

6.3. Intensive local studies

The intensive local field studies have focused on five major goals, including: (a) monitoring disease dynamics at local sites, (b) measuring seasonal variation in survival, and transition rates between asymptomatic and symptomatic states and vice versa, (c) identifying individual and environmental factors linked with infection risk, (d) quantifying host behavior thought to be important to disease spread—including movement and
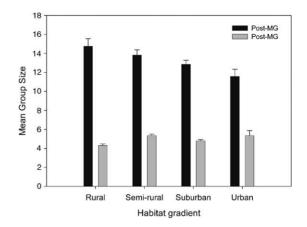

Fig. 5. House Finch group sizes, with 95% confidence intervals, from Project FeederWatch in an urban–rural gradient before (black bars, winter 1992–1993) and after MG became established (grey bars, winter 2002–2003) in the North-east. Note that before MG became established groups were larger in rural than in urban sites. After MG caused a severe decline in house finch abundance in the region group sizes became similar in all habitats, supporting the idea that MG mortality operated in a density dependent fashion (after Hochachka and Dhondt, unpublished manuscript).

social behavior, and (e) examining overall house finch health and co-infection with other parasites (Hartup et al., 2004). Our approach was to systematically capture house finches in local populations, mark them individually with unique color-band combinations, record their characteristics (e.g. age, sex, size, body condition, molt and breeding status, conjunctivitis score, MG serological status, co-infection, genetic traits), release them and conduct standardized re-sighting events. Color-banded birds can be identified without physical recapture (via resighting events) and disease state can be assessed visually with the use of binoculars or a spotting scope. By May 2004, we had obtained approximately 15,000 observations from about 4500 individuals in our data-base, with most data collected from Ithaca, NY, and additional observations from Madison, WI, and Atlanta, GA.

Local, intensive field studies have accomplished many critical goals, including many that extended beyond our initial objectives (Hartup et al., 2004). First, they allowed us to compare changes in prevalence at multiple field locations with broad-scale patterns from citizen science data, to ask whether the large-scale seasonal variation in prevalence as found by the HFDS (e.g. Fig. 4) reflects dynamics occurring in local
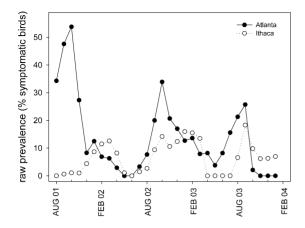
Fig. 6. Raw monthly prevalence of mycoplasmal conjunctivitis from field captures and re-observations of individually marked house finches in Ithaca, NY and Atlanta GA. Each individual is included only once in each disease state in each month. Note the high fall prevalence in Atlanta, the strong seasonal variation in prevalence in both locations, and the tendency for the fall peak to be earlier in Atlanta than in Ithaca. Sample sizes vary between 22 and 109 (mean 46.7 birds) per month in Atlanta, and between 29 and 379 (mean 174.3) in Ithaca.

populations, or if the large-scale patterns were simply generated by aggregating large quantities of data. To that end, we found that the pattern of local variation in disease prevalence is indeed similar to results obtained from the HFDS, in that prevalence is higher in Atlanta, GA (South) than in Ithaca, NY (North), and that there is a higher and earlier fall peak in prevalence in Atlanta as compared to Ithaca (e.g. Altizer et al., 2004a; Faustino et al., 2004). The second late-winter increase in disease prevalence, however, has not been observed in each winter in both locations (Fig. 6), suggesting that this bimodal epidemic pattern might be artificially generated by averaging HFDS data across many sites (although other explanations are possible).

Second, field studies have pointed out individual traits that influence disease spread, including host movement behavior, flocking behavior, and age. As such, during fall outbreaks, physical signs are substantially more prevalent in juvenile than in adult birds (Altizer et al., 2004a), indicating that juvenile birds might represent a major driving force behind the seasonal epidemics. A comprehensive CMR study further showed that apparent survival was higher in normal compared to diseased birds, and that transition rates between states (normal to diseased and vice versa) vary

with season and age (Faustino et al., 2004). Furthermore, field studies have provided definitive evidence that wild birds can recover from disease (Faustino et al., 2004), even after showing severe physical signs for 2 months or more, despite the fact that MG has a pronounced negative effect on the body condition of diseased birds (Altizer et al., 2004a).

Field observations have also underscored interactions between host behavior and disease spread. In particular, diseased birds are less mobile, have poorer feeding efficiency, and spend more time alone at bird feeders compared to healthy birds (Hotchkiss et al., in press, Hawley et al., unpublished manuscript). Although smaller flock sizes observed for diseased birds could reduce pathogen transmission opportunities, the fact that infected birds linger at bird feeders could effectively contaminate feeding stations to the point that they serve as major foci of infection for wild flocks.

Analyses of CMR data combined with radio tracking studies have generated key insights into house finch movement behavior and social dynamics. For example, in the Ithaca population we observed a high proportion of transients (birds trapped once, and never encountered again). These transients could facilitate spread of disease among sites (Faustino et al., unpublished manuscript), but this phenomenon also adds a complicating factor to analyses of local variation in prevalence and survival.

Observations of the social dynamics of house finches during the fall and winter showed that birds are faithful to social foraging groups, and that distinct social networks can inhabit overlapping foraging areas (Swarthout et al., unpublished manuscript). Thus, house finches around Ithaca are clearly spatially organized, although social group sizes are quite large (probably 100+ individuals), and some individuals move between groups. This can result in very large differences in disease prevalence at a fine spatial scale (see also Hochachka and Dhondt, unpublished manuscript). Interestingly, house finches that associate at night also associate during the daytime (Swarthout et al., unpublished manuscript). Moreover, counter to our initial expectations that house finches gather in large roosts at night, radio tracking studies showed that these birds in fact roost in small groups (mean 3, maximum 11: Swarthout et al., unpublished manuscript), suggesting that roosting aggregations might be less important to disease spread than we initially anticipated.

Finally, results from intensive field studies reveal critical issues that must be addressed by any disease project (including our own!) using field-based methods for monitoring the health status of wild populations; namely the assessment of disease status and the impact of variation in detectability between healthy and diseased individuals when quantifying prevalence. From one perspective, our results show that the presence of MG in eye samples is closely, but not completely correlated to the presence of physical signs (Hartup et al., 2001a; Kollias et al., 2004), and that information on antibody status, outward signs, and bacterial presence can provide conflicting information. This raises an important question about how to determine the true infection status of wild animals. In addition, CMR analyses showed that differences between normal and diseased individuals in both survival and encounter rates varied over time, leading to the conclusion that prevalence values calculated without correcting for variation in encounter rates between healthy and diseased individuals can provide an inaccurate description of prevalence in a population. This is a generally important result which probably applies to many studies of disease prevalence both in wild animals and humans (Faustino et al., 2004, Jennelle and Cooch, unpublished manuscript) (including purely observational data such as our House Finch Disease Survey) but corrections for disease-state effects on encounter rates are rarely performed (Jennelle and Cooch, unpublished manuscript), in part because of the large sample sizes, high encounter probabilities and systematic sampling required to correct for these biases.

6.4. Experimental studies in captivity

There were multiple objectives for the experimental studies conducted in captivity. We wanted to: (a) study the course of disease in individually housed birds in controlled conditions, (b) determine the effect of group living on infection and disease course (including infection and recovery probabilities), (c) determine how long infected individuals remained infectious, (d) determine factors causing inter-individual variation in response to infection, (e) demonstrate key modes of transmission, (f) study interaction with other parasites and pathogens, (g) describe disease pathology, (h) determine the persistence of MG in various tissues, (i) carry out dose–response studies, and (j)

determine the extent and duration of immunity after recovery from a first infection, and the persistence of antibodies.

Our initial results showed high morbidity but low mortality resulting from an infection of naive birds (Kollias et al., 2004). This outcome was surprisingly different from earlier published results that showed high morbidity and high mortality (Luttrell et al., 1998). In our study, we housed experimental birds individually in cages under controlled environmental conditions, which reduced stress during the experiments and probably explains this reduced mortality. Previously unexposed house finches experimentally inoculated with MG by eyedrop developed conjunctivitis 2–4 days after inoculation. Swelling and redness rapidly increased in severity through day 10 post-inoculation, followed by a gradual recovery 3 weeks post inoculation. As conjunctivitis developed, birds became inactive for up to 70% of the time, as compared to 0% before infection (Kollias et al., 2004). MG was detected by PCR from conjunctival swabs on average for 37 days, although in some individuals MG was still detected 21 weeks post inoculation, suggesting that a diseased bird could remain infectious for several months after infection. Finally, whereas most birds fully recovered, some individuals developed chronic conjunctivitis (Kollias et al., 2004).

Recovered house finches from this first experiment were re-infected with MG and developed conjunctivitis within 24 h, but most birds recovered rapidly, within 10 days. Surprisingly, birds re-infected 7, 10 and even 14 months after the initial infection developed similar physical signs. These signs were, however, much less severe than during a first infection, and disappeared much more rapidly (Sydenstricker et al., in press). One of the re-infected birds cleared MG within 24 h, and never developed physical signs. At the other extreme, one of the re-infected birds still had physical signs 2 months post-re-infection when the experiment was stopped (Sydenstricker et al., in press). Collectively, these results demonstrated that most recovered birds remain susceptible to re-infection but maintained partial immunity for more than a year.

Following the end of our first experiment, one bird spontaneously relapsed to express physical signs several months after recovery, and with no re-exposure to MG. To help explain this recrudescence

of infection (also observed in some 'recovered' wild house finches), we sampled for MG in diverse respiratory and extra-respiratory tissues of recovered or chronically infected house finches. Using Lauerman PCR, MG was detected in the trachea, spleen, liver and kidneys, also in individuals that showed no physical signs. This study demonstrates that MG is capable of dissemination to extra-respiratory system sites, allowing flare-ups to occur in immunosuppressed hosts (Sydenstricker, unpublished).

Histological evaluation of ocular lesions associated with mycoplasmal conjunctivitis showed variation in the ocular tissues including cornea, anterior uvea and the palpebral conjunctiva in birds differing in eye score (Njaa and Sydenstricker, unpublished).

House finches housed together in a group showed remarkable inter-individual variation in disease course (both latency to infection and daily recovery probability) when we infected a single individual and allowed secondary transmission to occur. This variation was possibly linked to social dominance (Hawley and Jennelle, unpublished) and to ambient temperature, which may help explain seasonal patterns. Since social behavior and temperature are linked in house finches, both may mediate the seasonal dynamics that we observe at small and large geographic scales.

One of the major challenges faced by this study has been to experimentally confirm various hypothesized modes of disease transmission. In the wild, house finches form large flocks at feeding sites. At feeders these birds exhibit intraspecific aggression, but analyses of video recordings show that although there is some contact between birds, this is rare (Jennelle, unpublished), suggesting that MG may not be primarily transmitted by direct contact. We also know that nocturnal roosting aggregations are smaller than daytime aggregations (see above), suggesting daytime feeding flocks as the primary source of disease transmission. We therefore experimentally tested the possibility of indirect transmission through fomites, and our initial results demonstrated that MG remained infectious for up to 12 h after feeders had been inoculated with swabs of bacteria (Sydenstricker et al., unpublished). Bird-feeders, therefore, could be a key vector of MG transmission among wild house finches, and could facilitate exposure of other bird species (see also Hartup et al., 1998).

6.5. Mathematical models

To generalize the results of our research, we are using quantitative predictive models to explore underlying processes that cause the observed dynamics of host and pathogen. Modeling continues to be an iterative part of the research program, with an initial set of models used to identify key processes from large-scale patterns (below and Hosseini et al., in press).

The MG–house finch system provides a striking example of how a relatively benign pathogen may have a significant impact on the abundance of its host. Long-term data on the abundance of house finches suggests that the arrival of conjunctivitis in a region leads to a rapid 50% decline in abundance (Hochachka and Dhondt, 2000). This effect is qualitatively similar to that predicted by a simple SEI model of the dynamics of conjunctivitis. This model divides the host population into susceptible, exposed and infectious birds; here we assume that exposed birds may transmit the pathogen, but at a lower rate ($\varepsilon\beta$) than infectious birds, which are at a later stage of infection and show overt visible physical signs of the presence of the pathogen. Infected birds remain in the exposed, subclinical stage for a time period, $1/\gamma$, and experience an elevated mortality rate, $\rho\alpha$, this is proportionately less than that experienced by visibly infectious birds, α; we also assume that infectious birds may lose their infection and return to the susceptible pool after a period, $1/\theta$. Alternatively, they may develop immunity, which eventually wanes before returning them to the susceptible pool. The dynamics may be described by three coupled differential equations which assume that the hosts settles to some steady equilibrium $(b - d)K/b$ in the absence of the pathogen, we assume this equilibrium is determined by the birth, b, and death, d, rates of the host, and the availability of resources such as food or roosting sites, designated, K.

$$\frac{dS}{dt} = b(S + E + I)\left(\frac{K - (S + E + I)}{K}\right)$$
$$+ \theta I - dS - \beta S(I + \varepsilon E)$$

$$\frac{dE}{dt} = \beta S(I + \varepsilon E) - (d + \gamma + \rho\alpha)E$$

$$\frac{dI}{dt} = \gamma E - (d + \alpha + \theta)I$$

When rates of transmission are relatively low and the pathogen has low levels of virulence ($\beta < 1$, $\alpha < d$) the model has relatively stable dynamics and settles to a steady equilibrium, N^*, E^*, I^* (note $S^* = N^* - E^* - I^*$).

$$I^* = \frac{\gamma E^*}{d + \alpha}$$

$$E^* = \frac{N^*(b(K - N^*/K) - d)}{d + \delta + \rho\alpha}$$

$$N^* = \frac{K((b - d) - c_1/c_2) \pm \sqrt{\beta^2 K^2 c_2^2 c_3^2 (2((d - b)} \times \sqrt{c_1/c_2 - bd) + 1 + b^2 + d^2 + 4c_1^2/\beta c_2 c_3 bK}}{2b}$$

where $c_1 = d + \delta + \rho\alpha$, $c_2 = (1 + \gamma/(d + \alpha))$, and $c_3 = (\varepsilon + \gamma/(d + \alpha))$.

Larger rates of transmission and significant levels of mortality produce sustained epidemic cycles; these are not observed in the house finch–MG system. Instead we observe a significant reduction in house finch abundance with no dramatic fluctuations in host abundance and pathogen prevalence (Fig. 7b).

This basic framework has been extended to further integrate results of field and laboratory experiments by incorporating several mechanisms that could be affecting the system, including seasonal breeding, winter flocking behavior, and duration and efficacy of immunity (Fig. 8). Thus, we found that the partial immunity demonstrated by experimental studies, combined with winter aggregation and pulsed breeding dynamics could be responsible for the annual peaks in prevalence we see at large scales. Although the presence of long-lasting immunity appears important, the fact that it may actually wane appears to have limited effect on large-scale dynamics. Partial immunity was incorporated into the standard SIR model (Anderson and May, 1979) by allowing recovered individuals to become re-infected, but forcing them to recover more quickly. We incorporated seasonal and latitudinal effects into breeding and social aggregation by incorporating forcing terms into these rates, which are usually constant. These forcing terms were estimated from relevant biological information, to the degree it was available (Hosseini et al., in press).
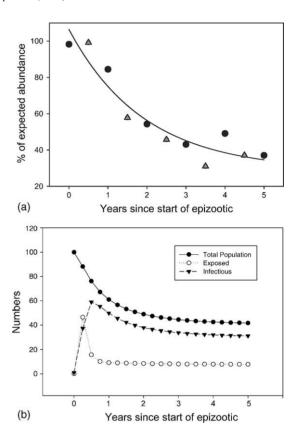

Fig. 7. (a) Change in house finch abundance in eastern North America after MG became established in a 2×2 degree block. Circles represent mean change in expected abundance in twelve 2×2 degree blocks where the disease threshold was reached in spring; triangles represent mean change in expected abundance in seventeen 2×2 degree blocks where the disease threshold was reached in the fall (after Hochachka and Dhondt, 2000). (b) Transient dynamics of a basic house finch model that assumes a local house finch population of 1000 birds has recently responded to the arrival of a single infectious individual. The total bird population is illustrated by the solid black dots, the numbers of exposed and visibly infectious birds by the open and solid red circles. We assume that transmission, $\beta = 0.5$, and that virulence leads to a doubling of background mortality, $\alpha = d = 0.5$. Birds are assumed to be in the exposed class for 3 months, and these birds have similar mortality to infectious birds, but only transmit the pathogen at half the rate of visibly infected birds. The relative decline in host abundance is largely determined by the magnitude of α and β, changes in the parameters determining relative pathology and transmission from exposed have little impact neither does the recovery rate of infectious individuals.

While not a perfect quantitative match, most of the qualitative features of observed dynamics appear to be captured by our current model. Following a process of eliminating mechanisms from the model, and exam-
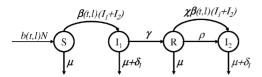
Fig. 8. Model Structure S represents susceptibles, I_1 individual infected for first time, I_2 individuals infected for second or more time, R recovered individuals, and N total population size. $b(t, l)$ represents seasonally and latitudinally forced birth rate, $\beta(t, l)$ seasonally and latitudinally forced transmission, γ recovery, μ background mortality, α additional mortality due to disease, and ξ factor representing extra increase in rate of recovery of partially immune individuals in the recovered class.

ining the dynamics without the mechanism present, we found that both seasonal aggregation and seasonal breeding were necessary for this model to predict the semi-annual peaks we see in the house finch–MG system (Altizer et al., 2004b; Fig. 4). Whereas other mechanisms besides seasonal aggregation could cause a seasonally forced transmission, the general idea that alternating intervals of seasonal breeding and seasonal transmission are important dynamical drivers of this system, and perhaps other systems, should be generally true. Furthermore, results from this model indicate that geographic variation in prevalence patterns (e.g. earlier and more severe fall epidemics in the South) could be caused by an extended breeding season in the southern part of the house finches' range relative to the extreme north.

This early framework has proved useful in directing field efforts on a local scale, focusing attention on the importance of host life history on disease dynamics—particularly seasonal breeding and seasonal variation in host social behavior. Well-mixed large-scale models will be followed by the development of more local and regional scale models, and these later models will incorporate local scale information to better understand how local dynamics scale up to regional ones.

7. Conclusions and priorities for future research

Understanding factors affecting the transmission dynamics of infectious diseases in natural populations has become increasingly important for wildlife conservation, particularly in light of human activities that increase the risks of disease emergence and severity of impacts (Daszak et al., 2000; Dobson and Foufopoulos, 2001). Among wild birds, for example, avian pox and malaria have been linked to marked losses in several native Hawaiian species (Van Riper et al., 1986; Van Riper et al., 2002). Most recently, American crows and related species in North America have died in unusually large numbers following the emergence of West Nile virus in 1999 (O'Leary et al., 2002; Hochachka et al., 2004). Yet, despite detailed studies of the dynamics of human diseases and increasingly sophisticated host–pathogen models, we know relatively little about factors driving changes in disease prevalence in wildlife populations (but see Hudson et al., 1998; Begon et al., 1999; Hochachka and Dhondt, 2000; LoGiudice et al., 2003; Harding et al., 2002) and processes that underlie host susceptibility to new and emerging diseases.

Consistent monitoring of mycoplasmal conjunctivitis in house finches at a continent-wide scale has provided an unprecedented opportunity to examine seasonal, geographic, and long-term temporal variation in the dynamics of this wildlife pathogen. The pronounced outward signs of bacterial infection have enabled us to involve large numbers of volunteers in our study who observed normal and diseased birds at their feeders. By combining different approaches, we have characterized large-scale patterns of disease prevalence, local-scale changes in prevalence, and have examined multiple ecological and behavioral processes that could underlie these dynamics. Identifying mechanisms and testing hypotheses requires both intense field studies and experiments with captive birds. These studies have also provided critical data for parameterizing mathematical models that summarize our current understanding of the system.

Thus far, our results showed—perhaps most importantly—that MG has persisted in eastern North American house finches for more than 10 years after the first appearance of the disease—and at relatively high average prevalence. We have also found evidence for:

- Remarkable geographic and seasonal variation in prevalence, with similarity among patterns generated by field and citizen science monitoring approaches.
- A likely effect of juvenile recruitment on seasonal epidemic pulses, and strong inference that geographic variation in the duration of the breeding

season mediates regional differences in the timing and size of outbreaks.

- A long duration of infection for both captive and wild birds, and a relatively high, but variable recovery rate of diseased birds.
- Partial immunity/protection among recovered birds, and evidence that some birds may be subclinical, and then relapse.
- Clear changes in the behavior and condition of diseased birds, including reduced activity, poorer feeding efficiency, more time spent at feeders, and more time spent alone or in smaller flocks.
- The existence of large daytime social groups that seem to be relatively site faithful in wintering house finches.
- At fine spatial scales, a surprising lack of synchrony in disease dynamics between adjacent social groups, probably caused by limited among-group dispersal and site or social group fidelity.
- Lower and variable survival and re-observation probabilities among diseased birds in the field, and seasonal changes in the difference in encounter rates between normal and diseased birds, resulting in problems of using raw prevalence observed in the field to describe true prevalence both in local populations and in large-scale surveys.

Interdisciplinary collaboration is crucial to advance our understanding of infectious disease ecology and evolution in wildlife populations—especially when dealing with complicated and poorly understood systems. Despite major progress outlined above, many questions remain to be resolved, particularly with respect to uncovering factors driving the dynamics of this system, and to methods of measuring true prevalence. We outline several priorities for research, some of these particular to the house finch–MG interaction, but many also remain as general priorities for uncovering processes important for wildlife–pathogen dynamics (Box 1). These questions include those related to (a) pathogen transmission and dispersal, (b) underlying determinants of host susceptibility, (c) ecological determinants of seasonal variation in prevalence, and (d) understanding the role of other host and pathogen species in this system.

In summary, we have learned that although our system is apparently a simple one (a single host, a single pathogen, direct transmission) understanding the cru-

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Box 1: Outstanding questions for future research

A. Issues related to pathogen transmission and dispersal
- Which transmission routes (direct contact, indirect contact, and vertical) are most important for disease spread, and what rates are associated with different mechanisms of exposure? Could arthropod vectors (mosquitoes or hippoboscid flies) contribute to disease transmission among house finches?
- What is the interaction between disease spread and group size, and do the details of social networks at fine spatial scales govern local and regional dynamics of disease?
- Does the rate of direct contact both within and between social groups and concomitant indirect contact at collective contact points (e.g. feeders) change seasonally and influence local scale disease dynamics?
- Do transients move the pathogen between social groups, and what is the impact of migration on disease dynamics at local sites?
- Do house finches carry the pathogen over long distances, and if so which demographic groups are responsible for long-distance spread?
- Where is the pathogen reservoir during summer months when birds with outward signs disappear, and what process generates rapid fall increases in prevalence?
- Is MG evolving in wild bird populations (molecular evolution), and have repeated introductions followed the initial emergence and spread? How are these developments impacting the epidemiology of disease?

B. Genetic and behavioral determinants of host susceptibility
- How important is social rank for exposure, development of disease, and host recovery?
- What is the relative importance of age, sex, and reproductive investment for individual variation in disease risk?

- How important is genetic variation and heterozygosity on susceptibility to disease?
- Has the host evolved in response to pathogen-mediated selection?
- How does individual immunity to MG relate to genetic variation at neutral and MHC genes?

C. Ecological determinants of seasonal and regional variation in prevalence
  - What are alternative scenarios for the double seasonal peak in prevalence, and how can we test them?
  - Does host immunocompetence vary seasonally or regionally, and does this variation impact disease dynamics?
  - How important are climatic factors for disease transmission, disease recovery, and impacts on host survival?
  - What factors generate differences in the timing and magnitude of epidemics observed among regions?
  - Does MG really undergo multi-year cycles, and what variables drive these longer term fluctuations?
  - How can parameter estimation from capture–mark–recapture modeling best be incorporated in SIR models?

D. The role of other host and pathogen species
  - Are co-infections with other parasites and pathogens important to disease susceptibility at the individual or population levels?
  - Are populations exposed to multiple pathogens more or less susceptible to a new disease?
  - What will happen in the Western U.S. where avian pox is much more prevalent than in the East?
  - Do other bird species serve as reservoirs for MG infections in the wild?
  - To what degree are other wild birds species exposed to MG through interactions with house finches, and does this represent a conservation risk? Can some of these other species represent reservoirs for MG?

cial mechanisms that drive the dynamics of our system requires studies at multiple scales and collaboration between specialists in multiple disciplines. Rigorous studies are needed to understand the ecological patterns and processes that govern them—and these studies are extraordinarily labor intensive. Our study would not have been possible without the major funding provided under the new multi-agency "Ecology Of Infectious Diseases" program. Our efforts have focused heavily on the interplay and correspondence between variables and processes in theoretical models and data from field and experimental studies. One of the enriching challenges in such multidisciplinary collaboration is the need to understand the vocabulary and the logic of colleagues trained in diverse disciplines—including field ornithologists, mathematicians, statisticians, behavioral ecologists, microbiologists, and wildlife veterinarians. This complexity and demand for interdisciplinary approaches are in part why ecological studies of the dynamics of wildlife diseases are at the same time both stimulating and rewarding, and why they are particularly interesting for participating graduate and undergraduate students.

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