Title: **The use and underuse of model systems in infectious disease ecology & evolutionary biology.**

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Abstract

Ever since biologists began studying the ecology and evolution of infectious diseases (EEID), laboratory-based 'model systems' have been important for developing and testing theory. Yet what EEID researchers mean by 'model systems' and what they want from them remains to be clearly delineated. This uncertainty holds back our ability to maximally exploit these systems, identify knowledge gaps, and establish effective new model systems. Here, we borrow a definition of model systems from the biomolecular sciences to assess how EEID researchers are (and are not) using ten key model systems. According to this definition, model systems in EEID are not being used to their fullest and, in fact, cannot even be considered to be model systems. Research using these systems consistently addresses only two of the three fundamental processes that underlie disease dynamics—transmission and disease, but not recovery. Further, studies tend to focus on only a few of the scales of biological organization that matter for disease ecology and evolution. Moreover, the field lacks an infrastructure to perform comparative analyses. We aim to begin a discussion of what we want from model systems, which would further progress toward a thorough, holistic understanding of EEID.

Introduction

Many researchers studying the ecology and evolution of infectious diseases (EEID) work on 'model systems', ourselves included. Yet, what we mean as a scientific community by a 'model system' is far from clear. The phrase 'model system' is invoked variously to mean that a particular experimental system is tractable (i.e., the host and/or parasite has a fast generation time, are easily culturable, and/or are easily manipulated (Antonovics et al. 2002; Ebert 2008; Koch and Schmid-Hempel 2011)); a model of a specific disease (Buckling et al. 1997) or studied with the goal of making some wider insight into general principles of host-parasite interactions (Antonovics et al. 2002; Huijben et al. 2018). Here, we take stock of what we do and, perhaps more importantly, do not do with 'model systems' in EEID. We do this not only to characterize the current state of model systems research in EEID, but also to stimulate discussion of whether this is what we want from model systems research and if not, to encourage the field to conceive of a clear and specific definition of what it should be.

The use, definition, and design of model systems is a matter for debate in several of the biological sciences but has perhaps received most attention in the biomolecular fields, such as genetics (Jenner and Wills 2007; Ankeny and Leonelli 2011; Katz 2016; Dietrich et al. 2019). In the biomolecular conception, model systems are a special subset of experimental systems that, first, are representative of species other than themselves and thus can be used to illuminate generalities about the focal phenomena of interest to a field (Ankeny and Leonelli 2011; Leonelli and Ankeny 2013). Second, model systems facilitate the study of multiple biological processes, from genetics to development to ecology, so that a holistic understanding of the focal organism or system is achieved (though it is rare in fact that the ecology or evolution of model organisms typically used in cellular-molecular-developmental research is well studied (Alfred and Baldwin 2015)). Lastly, model systems research is ultimately motivated by the aim of performing comparative analyses in order to reveal general rules about biology (Jenner and Wills 2007;

Ankeny and Leonelli 2011). As a result, an infrastructure for the sharing of data and resources is a key component of model systems research (Ankeny and Leonelli 2011; Leonelli and Ankeny 2013). It is notable that these notions of what makes for good (model systems) research from a cellular-molecular-developmental perspective echo the statement of Joseph Travis, in his Presidential Address to the American Society of Naturalists, that 'robust inference requires horizontal comparisons (the examination of the same questions at the same level in a variety of systems) and vertical integration (the study of many ecological and evolutionary processes as they unfold in a single species or system)' (Travis 2006).

Here, we use these criteria to frame an analysis and discussion of how we use (or underuse) systems that are employed as models in EEID. We do not claim these criteria to be the ultimate criteria that define a model system but rather use them as a benchmark against which to measure our use of so-called model systems. First, with reference to these criteria, we examine how a variety of systems considered to be 'models' in EEID are used by researchers. Second, where we are not meeting these criteria, we discuss whether this is or is not a loss—i.e., whether these gaps actually represent 'underuse' of systems. Lastly, we outline points that might be discussed so that the field can shed the definition of model system that scaffolds our review and build a bespoke definition for EEID.

Part I: The use of 'model systems' in EEID

To establish the extent to which the experimental systems in EEID are models *sensu strictu*, we conducted a review of the literature involving 10 experimental systems (Table 1).

Methodology

Key Phenomena

According to the definition of a model system outlined above, one distinguishing feature of a model system is that it is an experimental system in which the fundamental processes of interest to a (sub)discipline can be and are examined. So, to understand the extent to which experimental systems used by disease ecologists and evolutionary biologists are 'model systems', we need to first establish what processes or phenomena are of fundamental interest in EEID.

Theory provides an answer, by formally delineating the processes that drive disease dynamics. The vast majority of theoretical studies of infectious disease dynamics begin with some form of Anderson and May's models of disease dynamics (Anderson and May 1979; May and Anderson 1979). According to these models, a healthy, susceptible (S) host becomes an exposed (E) and then infectious (I) host by the process of pathogen transmission. During either of the infected states (exposed or infectious), hosts may experience disease. Hosts then exit the infected states via the process of recovery (or, in some cases, death) (Fig. 1A).

The phenomena of transmission, disease, and recovery are determined by both pathogen (Fig. 1A pink) and host traits (Fig. 1A, blue). In the case of transmission, whether a host becomes infected is dependent on, on the one hand, the pathogen's infectivity and, on the other, the host's susceptibility to infection. Once inside the host, parasites may replicate, so that the parasite population grows and/or develops to a new stage; for simplicity we term both of these 'replication' in our review. In the final stage of the infection, parasites may produce transmission stages (e.g., eggs or gametocytes, in the case of helminths and malaria parasites, respectively), which disperse from the primary host to a secondary host. The amount of disease a host experiences when it is infected depends on the virulence of the pathogen, here defined as the

parasite's contribution to disease, and immunopathology, when the host's immune response itself causes harm; the host's ability to minimize the damage associated with a given parasite burden is termed tolerance (Little et al. 2010). Lastly, recovery occurs either because the infection is self-limiting or because of the host's resistance, defined here as the capacity of the host to kill pathogens (as opposed to the opposite of susceptibility, as it is sometimes defined e.g. (Thrall and Burdon 2003)).

Each of the traits that govern transmission, disease, and recovery can evolve and can be influenced by ecological factors. Indeed, we outline the traits involved in each phenomenon in sequence and as pairs of host and parasite traits to emphasize the fact that coevolution occurs and can happen at several stages of the infection process (Duneau et al. 2011). In addition, at the level of the host or parasite population, the trajectory of trait evolution is determined, at least in part, by the presence and strength of trade-offs between the traits that govern the different phenomena. For example, the virulence-transmission trade-off that lies at the heart of models of parasite evolution (reviewed in (Cressler et al. 2016)), is determined by the relationship between within-host replication, virulence, and dispersal capacity.

In our literature review, we noted which of the traits that contribute to the key phenomena in EEID (Fig. 1A) were being studied. In some studies, it was not possible to isolate which of the transmission traits were being studied and/or multiple traits were assessed. For example, in a study of epidemic dynamics, the focus is not on parasite replication *or* infectivity *or* dispersal capacity but rather on the manifestation of these processes (what we call 'realized transmission'). In such cases, we used other terms (the definition of which can be found in Table 2) to classify what aspect of transmission was being studied. Similarly, many studies were not designed to tease apart the impact of (heritable variation in) virulence and tolerance on disease — i.e., they did not examine how disease changed when parasite strain was varied in a

single host genotype or when hosts of different genetic backgrounds were exposed a single parasite strain. We thus recorded only what symptoms (morbidity, mortality, etc.) were being monitored. Lastly, EEID researchers sometimes study other impacts of infectious disease, for example parasite nutrient content or the positive effects of parasites on hosts. These studies were allotted to an 'other' category. As we conducted our review, we tracked which of the traits that contribute to transmission, disease, and recovery were studied, how they were measured, and were alert to trends in research methodologies.

Focal questions in EEID & the scales of biological organization at which they are studied

Disease ecologists and evolutionary biologists are interested in the factors that drive variation in transmission/disease/recovery among individuals and populations, as well as the consequences of this variation (Box 1). The ecological interactions that impact trait variation occur at a variety of scales of biological organization (Lively et al. 2014); in turn, ecological interactions at a variety of scales can be impacted by infectious diseases (Fig. 1b). In addition to noting which of the key phenomena each study addressed, we therefore also recorded the scale of the phenomenon/trait being measured (i.e., the scale of the dependent variable) and the scale at which the variation was generated (i.e., the scale of the independent variable in the experiment). For example, in a study of the impact of population demography on the susceptibility of hosts, we recorded that the dependent variable (host susceptibility) was at the individual level and the independent variable (population demography) was at the host population scale. The details of which experimental variables were assigned to which scale can be found in Table 3 and Fig. 1b.

Systems reviewed

We examined which of these key phenomena were addressed using a variety of experimental systems (Table 1). In selecting these systems, we attempted to cover the history of the field, and a diversity of parasite types, from viruses to helminths, and host taxa, from plants, to

154 invertebrates, to mammals. So as to cover as great a breadth as possible, we set two criteria
155 determining whether a system could be included. The first was that researchers had to have the
156 ability to induce infection experimentally, since the capacity to manipulate the presence of
157 infections seems to be a basal requirement for their experimental study. We did not require that
158 the entire transmission cycle of the parasite could readily be completed in the laboratory since,
159 as we discuss more in the "Population & Epidemic Level" section below, doing so would have
160 severely restricted our ability to conduct this review. Second, the system had to be a focus of
161 ecological/evolutionary study for greater than ten years, since researchers cannot be expected
162 to have established a holistic study system in less time than that. Beyond that, we endeavored
163 to limit overlap between host or pathogen types.
164
165 By necessity, the list of systems (Table 1), though broad, is not exhaustive. First, we omitted a
166 number of important pathosystems where experimental inoculation of the host is possible but is
167 used relatively rarely compared to other research methodologies (at least in the corpus of
168 literature recovered by our search (Lively 1987; Alexander 1989)). This was the case for the
169 snail-trematode system *Microphallus-Potamopyrgus*, for example, which has made an important
170 contribution for our understanding of host-parasite coevolution (Dybdahl and Lively 1998; Lively
171 and Dybdahl 2000; Morran et al. 2011). Second, we omitted bacteriophage-bacteria systems,
172 though they permit experimental inoculation of hosts and have made a substantial contribution
173 to our understanding of host and parasite (co)evolution and pathogen emergence (Horne 1970;
174 Chao et al. 1977; Lenski and Levin 1985; Benmayor et al. 2009; Koskella 2014). Given the
175 myriad host strain-phage combinations utilized in this subfield, this literature was unwieldy to
176 review; it deserves a standalone review that can also address the specific biology of virus-
177 bacteria interactions. In addition to systems where experimental inoculation is possible, we
178 acknowledge that there are several pathosystems where infections are not experimentally
179 generated routinely but nonetheless have made important contributions to our understanding of

disease dynamics (Hudson and Newborn 1998; Ezenwa and Jolles 2015), as have observational studies or field experiments in systems we did review, such as those involving *H. polygyrus* (Gregory et al. 1990; Knowles et al. 2013). Since we sought to investigate *trends* in EEID, and those we recovered seemed relatively constant, however, we believe the omission of these systems does not greatly impact our results.

Literature search protocol

We searched for scientific literature related to each system using Web of Science (Thomas Reuters). We searched for the scientific name of the pathogen, including nomenclature that had been previously used but since abandoned; for example, in the case of the *Heligmosomoides polygyrus*, we also searched for *Nematospiroides dubius*. We identified the 10 most cited and 5 least cited studies that included at least one laboratory-based experiment in which hosts were exposed to the pathogen (even if that was the inoculation of hosts prior to their dispersal into the field or laboratory-based phenotypic assessment of field collected material). Least cited papers were included not only because they were likely to include the most recent research but also because personal experience has taught us that these papers contain some of the oldest and/or most idiosyncratic research, and so could reveal ideas once pursued in EEID but since abandoned. In the case of some pathogens that are also important model systems in other fields, e.g., the rodent model of poxviruses, infectious ectromelia virus, and the rodent intestinal roundworm, *Heligmosomoides polygyrus,* the top ten/bottom five cited papers did not address ecological and evolutionary questions. When this occurred, we performed an additional search to subset out papers of an ecological or evolutionary nature, by searching for 'ecolog* OR evolution*' in the topic field in addition to the pathogen species name.

Lastly, to further capture older research, we identified one scientist who pioneered the study of each model system that we reviewed (Table 1, we list several researchers for completeness but

only the research of the bolded researcher was searched for). When fewer than five papers by the 'founder' appeared in the first search, a second search was conducted with the system name(s) and the name of the scientist. We added the most cited references that appeared in this secondary search to our primary search results, leading to a total of five papers by the `founder' in the final collection of papers for the system. In the case of infectious ectromelia virus, it was clear that Web of Science did not retrieve historical references since it uncovered some, but not all, of a set of research articles conducted by the system's 'founder' Frank Fenner, which were numbered in sequence. We thus searched for this author's bibliography directly, to recover the missing papers from this sequence. That Web of Science did not uncover these older references highlights that there are limitations associated with using this (or indeed any other) search engine for this review. As the field of EEID became distinct from its relatives around the time that Anderson and May published their landmark papers, and the majority of systems reviewed here were established as experimental systems at that time or afterward (Table 1), we do not think this greatly impacts our conclusions, however.

With the papers collated, we then extracted the following information from each paper: i) which of the umbrella phenomena (transmission, disease, recovery) was investigated, ii) the variable(s) manipulated, iii) the variable(s) measured, and the scale at which these variables were measured or manipulated (see '*Focal questions in EEID & the scales of biological organization at which they are studied',* above).

Results

We present the results of our review with a focus on the extent to which those systems used as models in EEID address the key phenomena of interest to the field — transmission, disease and recovery — and the extent to which we study them at the biological scales at which disease dynamics occur. As such we seek to understand the extent to which model systems are studied

holistically and are representative of the processes EEID researchers are interested in. Where possible, we highlight specific features of the different systems that enable disease ecologists and evolutionary biologists to study certain phenomena in them.

1. Are we studying the key phenomena in EEID?

All of the key phenomena — transmission, disease, and recovery — are represented in the studies reviewed. However, the extent to which all three of the phenomena are addressed varies among systems, as does the extent to which they are used to study the traits that drive these key phenomena (Fig. 2a).

Transmission

Transmission was the most studied phenomenon, being the focus of more than 80% of the studies reviewed. However, the parasite traits involved in transmission (Fig. 1A) were not equally represented (Fig. 2a). Infectivity and replication/development were well represented, being the focus of approximately 25% and 30% of the studies of transmission, respectively. However, only ~10% of the studies reviewed focused on the capacity of parasites to exit the host, for example via the production of transmission stages. A similarly small proportion followed the infection from its initiation to onward transmission ("realized transmission"). Although realized transmission was studied in 7/10 pathosystems, it was only a regular focus of study (i.e., the focus of >=20% of the papers) in four systems: IEV, *C. bombi, D. spathaceum,* and *R. ondatrae*. Notably, the system in which realized transmission was most often studied — IEV — is no longer in use as an experimental system in EEID, somewhat ironically because it was so transmissible as to be considered a biohazard (Fenner 2000)! Rather than measure transmission directly, most researchers took pathogen load as a proxy for it.

In addition to parasite traits, transmission also involves host susceptibility, narrowly defined here as the capacity of a host to become infected. Of those reviewed, *M. lini* was the system most used to study susceptibility, which is fitting given its role in the development of the gene-for-gene model of susceptibility/infectivity (Flor 1971). The genetic component of susceptibility and how it varies in space and time was the major focus of studies employing *M. lini* and *P. ramosa,* which also coevolves with its host through the matching of genes that mediate infectivity/ susceptibility (Thrall et al. 2016). Interestingly, no studies of recovery/resistance in *M. lini* and *P. ramosa* appeared in our search. This could imply that there is either an evolutionary trade-off between defenses that block and clear infection (why invest in resistance if you don't get infected, after all?) or, recognizing that we reviewed only a subset of papers published in each system, this might reflect the relative degree to which different topics have been studied and/or cited. Indeed, we know there are studies in *P. ramosa* that have focused on post-infection resistance (e.g., (Hall and Ebert 2012)). In addition to the genetic basis of susceptibility, the behavioral component of host susceptibility was also examined, primarily in the *D. spathaceum* and *C. bombi* systems (Hernandez and Sukhdeo 1995; Karvonen et al. 2004; Gegear et al. 2006; Bouwman and Hawley 2010; Milotic et al. 2017; Fouks et al. 2018; Mikheev et al. 2019).

Disease

The negative impact of infection on hosts, which we define as disease, was the focus of more than half of the studies that we assessed and was investigated in all systems. Surprisingly, despite their conceptual importance in disease ecology, virulence and tolerance were the focus of fewer than half of the studies of disease. Disease is a manifestation of the interaction of the host and parasite; here, we use "virulence" to denote the parasite's contribution to disease, and "tolerance" to denote the amelioration of that effect by the host. Approximately a sixth of the studies of disease focused on virulence, fewer than 5% on tolerance. Studies of virulence were conducted in five systems. Of these, genetic variation at the level of both the host and the

283 parasite was exploitable for laboratory study in two systems, *M. gallisepticum* and *P. chabaudi*.
284 This permitted the quantification of heritable variation in tolerance and virulence to disease in
285 the same system, a necessary precursor for studying the coevolution of these traits (Little et al.
286 2010) (though how relevant that is in the *P. chabaudi* system, in which the host and parasite do
287 not naturally cooccur, is questionable). In the majority of studies of disease, the contributions of
288 host and parasite genetic variation to variation in disease severity was not the focus. Rather,
289 these studies focused on describing the symptoms of infection (e.g., (Weimer et al. 1955;
290 Goodman and Johnson 2011)) or how they change with the host environment (Ferguson and
291 Read 2002; Paull and Johnson 2011; Overholt et al. 2012).
292
293 Disease was measured using qualitative and quantitative measures of varying ecological and
294 evolutionary significance. In some systems, like *P. ramosa* — which is a castrating obligate-
295 killer of short-lived and rapidly reproducing zooplankton — the impact of infection on survival
296 could be directly assessed (Ebert 2008). In others, disease was measured via quantitative
297 health metrics such as cellular numbers, as in *P. chabaudi*, or via a qualitative metric, as in *M.*
298 *gallisepticum,* where the severity of conjunctivitis in birds was measured via an 'eye score'
299 (Kollias et al. 2004). In relatively long lived animals, such as mice, fish, and birds, it is difficult to
300 know how these measures translate into life-long fitness (Graham et al. 2010), though our
301 search did uncover studies where symptom severity was related to the likelihood that hosts
302 were predated upon (Seppälä et al. 2004, 2005). Furthermore, in a number of systems the
303 effect of infection on behaviors directly related to fitness, such as mating (Kavaliers et al. 2003),
304 foraging (Crowden and Broom 1980; Ponton et al. 2011; Adelman et al. 2015) and predation
305 (Webster et al. 2000), was assessed. It is notable that, in the studies we reviewed, the effect of
306 infection on hosts' susceptibility to predation was only assessed in systems where parasites are
307 trophically transmitted (*D. spathaceum* and *H. diminuta*) and, as such, these studies were as
308 much studies of the fitness of the parasite as the host.

Recovery

Recovery was the least well studied of the three key phenomena, the focus of just 16% of the studies, although it was studied in the majority (7/10) of systems. The rarity of studies is likely to be in part because we have allotted only one trait to the phenomenon of recovery — resistance, defined narrowly as the capacity for hosts to kill parasites once they have infected the host. It is notable that resistance, thus defined, does not equate to recovery in the vast majority of the studies reviewed. This is because hosts routinely recover from infection in only 4/10 of the systems: IEV, *H. polygyrus, P. chabaudi,* and *M. gallisepticum* (Table 1).

In the vast majority of these studies, resistance was measured by quantifying the reduction in parasite load after the infection was established. As such, whether the host was involved in the clearance of parasites (per the above definition of resistance) or whether parasite populations were self-limited (which itself could be host-induced (Hite et al. 2019; Wale et al. 2019)) was not always delineated. The host immune response to infection was measured directly in *H. diminuta, H. polygyrus, D. spathaceum,* IEV, *M. gallisepticum,* and *P. chabaudi* and these same systems are those in which the host response can be manipulated (usually by pre-exposing hosts to the pathogen). It is likely that such 'mechanistic' studies of resistance/recovery are possible in these systems because they involve vertebrate hosts whose immune system is relatively well characterized. Interestingly, though one of the oldest studies of *D. spathaceum* is mechanistic in nature (Stables and Chappell 1986*a*), and the system was established by parasitologists/immunologists, it was not used for mechanistic studies of the host response in any other study reviewed. Rather, *D. spathaceum*, along with *C. bombi*, was used to investigate how factors beyond the individual host impact the host's capacity to control infections, including abiotic factors (Stables and Chappell 1986*b*; Palmer-Young et al. 2019), social group-composition (Klemme and Karvonen 2018) and socially transmitted microbes (Koch and Schmid-Hempel 2011; Koch and

334 Schmid-Hempel 2012); however, these studies were not included in the recovery category, because
335 they do not address innate host resistance.
336
337 **At what scales are we studying key phenomena?**
338 Approximately a third of the studies involve researchers looking at how 'individual level' factors
339 — e.g., parasite strain (Fenner 1949*a*; Rodriguez and Kleven 1980), host age (Fenner 1947*a*)
340 or immune status, size of parasite inoculum (Fenner 1947*b*; Johnson et al. 2001; Karvonen et
341 al. 2003), or inoculation method (Fenner 1947*b*; Lepak and Thatcher 1962) — impact individual
342 level variables. Since the majority of studies do not focus on interactions between individual-
343 level processes, we focus on other scales from here on. Each scale is first addressed in its
344 capacity as a dependent and then an independent variable; some studies appear in multiple
345 categories. To stimulate future research, we identify challenges involved in doing research at
346 these different scales.
347
348 *Within-host*
349 Within-host processes were either manipulated or measured in just over a third of the studies
350 reviewed. The dynamics of parasite populations and their distribution within the host
351 were the subject of the earliest papers regarding *D. spathaceum* (Betterton 1974), infectious
352 ectromelia virus (Fenner 1947*a*), *H. diminuta* (Chandler 1939), and *H. polygyrus* (Dobson and
353 Owen 1978) that our review uncovered. Approximately a quarter of all studies reviewed had
354 within-host dynamics as the response variable. These addressed the way that within-host
355 dynamics changed with parasite population parameters, such as initial size and genetic
356 background, and host factors such as immunity, diet (Bansemir and Sukhdeo 1996; Ponton et
357 al. 2011), and even temperature (Stables and Chappell 1986*a*).
358

Interactions among parasites was a major theme of studies in the within-host processes category. The majority of experiments we reviewed focused on intraspecific interactions and interrogated the (dis)advantage of focal parasite traits, including virulence, drug resistance, and motility, in different host environments. Variability in host environments (and hence within-host interactions) was created by modulating intrinsic host traits such as host sex (Gipson et al. 2019) or via the administration of medications (Wargo et al. 2007; Huijben et al. 2015). Interspecific interactions were similarly, though less often, explored (Holmes 1959; Graham et al. 2005; Lass et al. 2013; Budischak et al. 2015). Some of the more recent studies in the corpus of papers we reviewed focus on the interaction between parasites and the microbiota, rather than on parasite-parasite interactions (Koch and Schmid-Hempel 2011; Koch and Schmid-Hempel 2012; Clerc et al. 2015; Zaiss et al. 2015). Interestingly, these papers were often focused on the use of parasites to alter microbiota to promote host fitness; in contrast, of the papers in our review that focused on parasite-parasite interactions, the predominant focus was on parasite fitness.

Studies of within-host processes are often dynamical in nature and thus necessitate the tracking of host or parasite populations within the host's body. In the majority of study systems, the dynamics of within host populations were tracked by the sequential culling of cohorts of animals. The exceptions were *M. gallisepticum* and *P. chabaudi,* in which non-destructive, repeated sampling of parasite and disease parameters (conjunctivitis and anemia, respectively) from single individuals was possible. The capacity to sample in this manner is likely facilitated by these pathogens falling at extreme ends on a gradient of tropism: *Plasmodium chabaudi* is distributed in the blood (at least during the asexual stage of infection), so one can sample the periphery without destroying the animal; *Mycoplasma gallisepticum*, by contrast, is concentrated in and around the eye (though it can be found elsewhere (Dhondt et al. 2005)).

385 *Population & Epidemic Level*

386 The study of epidemiological dynamics, either as an independent or dependent variable, is
387 undertaken rarely in the laboratory; only 14% of the studies reviewed address disease dynamics
388 at this scale. This implies that the rarity of studies of realized transmission at the individual level
389 might be due to difficulties with the initiation of transmission in the laboratory, rather than to the
390 relative ease of measuring parasite load, as compared to realized transmission. Indeed, in half
391 of the systems the entire transmission cycle of the parasite cannot be readily completed in the
392 laboratory (Table 1), ruling out the study of epidemic dynamics and their subsequent impacts on
393 parasite and host population dynamics.

394

395 Two systems dominate the study of epidemiological dynamics, IEV and *C. bombi.* IEV is the
396 focus of the earliest epidemiological investigations in our review, which focus on describing how
397 'individual' level variation of host and parasites, such as strain, age, and immunity, impact
398 epidemics (Fenner 1948*a*, 1948*b*, 1949*b*). By contrast, those studies involving *C. bombi* focus
399 on the impact of features of the host population, specifically density (Bailes et al. 2020),
400 structure (Otterstatter and Thomson 2007), relatedness (Shykoff and Schmid-Hempel 1991),
401 and turnover (Buechel and Schmid-Hempel 2016), on epidemic dynamics. The experiments that
402 utilize *C. bombi* involve many more replicates than those using IEV, presumably because they
403 involve smaller, invertebrate organisms whose populations can be established in replicate
404 without as much maintenance or as many ethical concerns. This feature also makes epidemic
405 level studies possible in the *P. ramosa* system (Ebert et al. 2000). It is notable that the
406 evolutionary impact of epidemics was not examined in any of the studies we reviewed.

407

408 Importantly, in several of the systems reviewed, laboratory studies were conducted alongside
409 studies of population/epidemic scale processes in the field. Such field studies facilitate the study
410 of (co)evolutionary dynamics (Thrall et al. 2002; Ebert 2008; Bonneaud et al. 2018) that, in turn,

411 further laboratory investigations. For example, approximately half of the studies of the effect of
412 population variability on individual-level infection traits were conducted using *M. lini* and *M.*
413 *gallisepticum*. In each of these systems, spatial dynamics of epidemics in the field drove
414 parasite and host evolution that was then exploited to study the heritable variation in infectivity,
415 virulence, and immunity in the laboratory (Hawley et al. 2013; Bonneaud et al. 2019). *P. ramosa*
416 provides similar opportunities to sample a diversity of pathogens and hosts, as well as to
417 analyze the effect of epidemics on host evolution (Duncan and Little 2007).
418
419 *Community level*
420 The interchange between interactions at the community level and the dynamics of infectious
421 diseases comprised ~10% of the studies reviewed. With the growing importance of zoonotic
422 diseases as a public and animal health problem, how parasites move between multiple hosts
423 and why some hosts support pathogens but others do not has been the focus of high-profile
424 EEID research in recent years (Johnson et al. 2012, 2019; Mollentze et al. 2014; Fenton et al.
425 2015; Olival et al. 2017). It was surprising, then, that in only 6% of the studies reviewed was the
426 variability of infections in different host species examined. The question of why some hosts are
427 'better hosts' than others was specifically addressed in *H. diminuta* (Read and Voge 1954;
428 Johnson et al. 2012) and *R. ondatrae* (Johnson et al. 2012); the former study was one of the
429 oldest of all those reviewed. As an aside, the variation of infections among different host
430 *genotypes,* which might be considered a topic analogous to host-species variation, was a focus
431 of a further ~10% of studies reviewed (these were not counted as 'community' level studies). Of
432 these, two studies distinguished themselves by using experimental evolution rather than a
433 standing trait variation to study host-range (Dobson and Owen 1977; Brindley and Dobson
434 1981).
435

In addition to studies focused on the effect of the host's identity on disease dynamics, further studies investigated how the community of hosts, specifically its composition, altered disease dynamics. There was only one study in which the impact of parasites on the formation or function of ecological communities (as opposed to the other way around) was the focus. Specifically, Yan *et al*. investigated the impact of *H. diminuta* on interspecific competition (Yan et al. 1998).

Other community-level studies focused on the interaction of parasites and predation (likelihood) in trophically transmitted systems. Interestingly, one of these studies (Morgan et al. 1997) focused on the vulnerability of the parasite rather than the host to predation.

Indeed, there were a few studies that investigated how parasites withstand the ecological environment outside of their host. Of these, all but the aforementioned study focused on abiotic factors, including light, temperature, humidity, and solar radiation (Flor 1958, 1960; Voge and Heyneman 1958; Voge 1959*a*, 1959*b*; Overholt et al. 2020; Rogalski and Duffy 2020). Those studies that were of an ecological nature — Flor's studies of the impact of X-ray radiation on *M. lini* were not motivated by an interest in radiation *per se* but in the mutations that resulted from it — were conducted using *H. diminuta* and *P. ramosa* and were, respectively, some of the oldest (1950s) and newest (2019-2020) studies reviewed. It is likely that studies of parasites in the environment are a rarity in our review because EEID researchers are often most interested in *interactions* between host and parasite, of which disease is the most obvious manifestation, rather than parasites alone.

Ecosystem level

Given the lack of epidemiological-level studies and that we were focused on studies with at least one laboratory-based experiment, it is perhaps unsurprising that few studies address

ecosystem-level impacts. Just two of the studies reviewed, both of which involve *R. ondatrae,* can be considered to be truly focused on ecosystem processes: one examines the impact of elemental nutrient supply on pathogen spread (Johnson et al. 2007), the other the nutritional value of individual parasites for consumers (McKee et al. 2020). Another study of the chemical/nutritional analysis of parasites, which was conducted over four decades before the latter and used the *H. diminuta* system, was also recovered in our review (Roberts 1961). However, the results of this study — though eminently relevant to ecosystem processes — were interpreted in the context of their relevance to host-parasite interactions within-host rather than to ecosystem processes.

To what extent are we studying our systems holistically?

A goal of model systems research *sensu strictu* is to study all of the key phenomena that drive the focal process of interest. Disease dynamics are not only influenced by ecological interactions that occur at multiple scales (within-host, epidemic, etc.; Fig. 1B) but interactions that occur at one scale may have a dramatic impact on those at another. However, our review suggests that the effect processes at different scales have on one another are rarely studied.

There are two important trends regarding this lack of focus on interactions of processes at different levels. First, there is an absence of studies on how within-host or individual-level variation impacts population and ecosystem level processes (Fig. 3, bottom left of panels). Similarly, studies rarely examine how ecosystem- or community-level variation impacts population- or ecosystem-level processes, respectively. These trends are unsurprising given the rarity of studies at the population/epidemic level, as discussed above, and the overall lack of work on infectious diseases at the ecosystem-level (Preston et al. 2016).

Though it is uncommon to study how processes at 'small' scales impact 'large' scale processes (and vice versa), processes at multiple scales are varied in most systems (i.e., the top two rows of fig. 3 are often filled in many cells left to right, at least up to 'population' processes). It is most common for processes within hosts, at the individual level, and the host environment to be varied within a single system. Presumably, this is because these scales can be varied using individual hosts in the laboratory (e.g., one could inoculate an individual host with multiple parasites or remove parasites using antimicrobial drugs, vary the strain of parasite, and alter the husbandry of hosts). That there is consistent focus on the (interactions between) small scale processes among systems suggests that there is significant potential for their horizontal integration.

So, to what extent are our experimental systems model systems *sensu strictu*?

Our review of the most and least cited studies of the dominant model systems in EEID revealed that these 'model systems' are more 'experimental systems' — i.e., they are used to investigate particular phenomena or processes as opposed to systems used to establish a holistic understanding of the EEID (Ankeny and Leonelli 2011). While we address both transmission and disease in the laboratory, the third key process of interest to EEID, recovery, is often left unaddressed, not least because we often use systems in which it does not occur. In terms of the scale of interactions that these experimental systems are used to explore, researchers succeed in building a holistic understanding of host-parasite interactions at the level of the individual host (or parasite strain). Ironically for a field founded in population biology, however, we fail to scale up these studies to that of populations and above, at least in the laboratory.

Part II: The underuse of 'model systems'?

In the previous section we used the definition of model systems borrowed from the biomolecular sciences to investigate how we use experimental systems in EEID and, by extension, how they

are not used. To understand whether the gaps identified should be filled, we must assess whether these gaps hold back our understanding of EEID and, if so, if and how they could be remedied. That is, we must assess the extent to which our experimental systems are indeed underused.

The transmission gap

Since onward transmission is the ultimate realization of pathogen fitness, its relative rarity as an experimental outcome is notable. However, at least in the case of individual level studies their relatively rarity may not amount to an omission. Experimental proxies of onward transmission can be an appropriate measure of parasite fitness and allow for experiments with large numbers of individuals. For such proxies to be of maximal use in the analysis of parasite fitness, these proxies must be measured at the level of the individual parasite-host strain combination (e.g. (Bell et al. 2012)) and in circumstances that reflect natural transmission, deviations from which can dramatically change important measures of parasites fitness such as growth rate and virulence (Fenner 1947*b*; Spence et al. 2013), and thus projections regarding the trajectory of pathogen evolution.

The major limitation of using systems where the parasite cannot complete its life cycle in the laboratory (Table 1) is that it reduces the capacity to study epidemiology experimentally, something that was once a priority of EEID and arguably deserves concerted investment. Experimental studies of the epidemiology of IEV were important in the conception of the Anderson and May's classic models of infectious disease dynamics (Anderson and May 1979). Around the same time that those classic models were published, Anderson and colleagues led a push to develop new systems with which to study experimental epidemiology, including the *H. diminuta* (Keymer and Anderson 1979), *Gyrodactylus* sp. (Scott and Anderson 1984), and *H. polygyrus* (Keymer 1985) systems. Indeed, in 1985, Keymer wrote a manifesto of sorts,

539 outlining why epidemiological study systems were required and what they should look like
540 (Keymer 1985) — arguments that stand the test of time and resonate with the arguments made
541 herein. She argued that experimental epidemiological systems must allow the collection of data
542 on 'the complete epidemiological behavior of the parasite in its host population' (i.e., epidemic
543 level data), and 'the experimental study of population parameters …their dependence on, and
544 interactions with other biological processes and…physical variables' (pg. 56) (i.e., individual, ex-
545 host level data). That is to say, with such a system, one can isolate the effect of factors
546 predicted to influence epidemic dynamics (e.g., host genetic variability), tease apart how
547 combinations of factors manifest as epidemiological dynamics, and model variation that does
548 not (yet) appear in nature. Indeed, experimental epidemiological studies could represent an
549 additional, complementary source of high-quality data that could be used to widen the canon of
550 theoretical epidemiology, which is dominated by diseases that are viral, acute, and often target
551 juveniles (Keeling and Rohani 2011). As such, experimental epidemiology can not only help to
552 reveal the mechanisms underlying the dynamics we observe in nature but illuminate what could
553 be possible in nature, in all its diversity.
554
555 *Filling the transmission gap could boost 'vertical integration' in EEID*
556 A further advantage of boosting the capacity to study epidemics in the laboratory is that it will
557 permit the mechanistic investigation of feedbacks between 'small scale' within-host processes
558 and 'larger-scale' epidemiological processes; that is, it will fill the bottom left of the heatmaps in
559 Fig. 3. The study of interchange between processes at these scales has been the subject of
560 much recent theoretical investigation but is difficult to achieve in the field (Day et al. 2011;
561 Mideo et al. 2013*a*, 2013*b*). Take the evolution of drug resistance as an example. Recent
562 theoretical studies have suggested that, depending on the prevalence of circulating strains,
563 within-host competition might alter the selective benefit of using different drug-dosing regimens
564 (Hansen and Day 2014). Manipulating dosing regimens and/or epidemiological parameters can

565 be unethical and extremely difficult in human populations, wthere are also considerable
566 challenges distinguishing between *de novo* or acquired resistance. So, an experimental system
567 in which one could track the population dynamics of parasites within-host, as well of those of
568 hosts and parasites at the epidemic scale, would be invaluable in testing and expanding this
569 theory.
570
571 The development of systems in which we can study the interactions and feedback between
572 processes at the within-host and population scale (and even at larger scales) may be inherently
573 difficult, however, because the traits that make it good for one come at the disadvantage of the
574 other. On the one hand, to facilitate the study of epidemic dynamics, hosts must be small
575 enough that replicate, dense populations can be established, housed long-term, and
576 manipulated. On the other, the study of within-host dynamics over time in individual hosts
577 requires that hosts be robust enough to be repeatedly handled and sampled. Pathosystems of
578 large insects of agricultural importance may fall into this crucial 'sweet spot'. Indeed, early work
579 with *Tribolium* contributed to the understanding of the dynamics of host and parasite populations
580 (Park 1948; Keymer and Anderson 1979), and they have recently been established as an
581 ecological-evolutionary-immunological model (Tate and Graham 2017; Jent et al. 2019). As
582 Keymer pointed out years ago (Keymer 1985), vertebrate models of human disease are well-
583 placed for this work, since much is known about vertebrate immunity; the development of tools
584 to non-invasively track infection dynamics (e.g. quantitative PCR, *in vivo* imaging) and
585 manipulate parasite and host genetics since then, have only added to their advantages.
586 (Keymer 1985)Recent studies in which laboratory mice were 'rewilded' in order to understand
587 the relative contribution of environment and genetics to within-host interactions (Lin et al. 2020;
588 Yeung et al. 2020) demonstrate the unique utility of laboratory mice for answering questions in
589 disease ecology. Such studies might be extended to study the interchange between within-host
590 and epidemic dynamics, if technologies that permit cheap, regular, high-throughput sampling of

591 individuals could be developed. These studies also demonstrate that it is possible for leading
592 model systems in biology writ large to also be powerful systems for EEID research.
593
594 While it is clear that laboratory studies could be better harnessed to understand disease
595 dynamics at or below the epidemic scale, it is not immediately obvious that they could illuminate
596 epidemic processes at the scale 'above' epidemics, especially the ecosystem level. Such
597 experiments would necessitate the use of micro- or meso-cosms e.g. (Johnson et al. 2007).
598 However, the suitability of these types of experiments for the study of ecosystem-level
599 processes has drawn repeated criticism because often even very large mesocosms are
600 incapable of capturing the spatial or temporal scale of the processes of interest, the diversity of
601 organisms involved (particularly those at higher trophic scales), or physical/chemical structure of
602 environments (Carpenter 1996; Schindler 1998). It may thus be best to reserve mesocosm-
603 scale experiments for estimating parameters of mathematical models (e.g. the biomass of
604 pathogens or the (change in) nutrient content of infected hosts) or to use them only where
605 ecologically-relevant effects are likely to be observed e.g. in systems that involve pathogens of
606 ecologically dominant hosts species and simple, linear food webs (Mitchell 2003; Duffy 2007;
607 Borer et al. 2009).
608
609 *Toward the cryptic & rare*
610 Our review suggests that we are not using our model systems to their full potential for the study
611 of interactions between parasites and host immunity and their contribution to eco-evo dynamics
612 of disease. Of the studies we reviewed that addressed infections that do not resolve, few used
613 measures of infection 'success' that permit the investigation of host defenses other than those
614 that make the host refractory to infection. For example, in studies of *D. spathaceum, P. ramosa*,
615 and *R. ondatrae*, parasite 'infectivity'/host 'susceptibility' was often measured as the proportion
616 of hosts who bore parasites at the site from which the parasites leave the host. This measure

617 confounds the processes of parasite infectivity with those of development and migration and, on
618 the other hand, suggests that there is no host defense other than that which prevents infection
619 in the first place. However, host responses that destroy parasites after the parasites
620 successfully penetrates the host are present in these systems (Hall and Ebert 2012; LaFonte
621 and Johnson 2013). Methods for explicitly measuring a parasite's progress through the host e.g.
622 imaging of fluorescent parasites (e.g. (Duneau et al. 2011; LaFonte and Johnson 2013) and
623 mathematical models that can quantitate how the hosts resist and tolerate infection (e.g. (Wale
624 et al. 2019)), could refine our understanding of which traits mediate parasite and host fitness at
625 each stage of the infection (Duneau et al. 2011). Indeed, there is much to gain from the
626 methodologies used in cellular-molecular biology, such as fluorescence-based microscopy and
627 cytometry, as well as that field's mechanistic understanding of host-pathogen interactions. By
628 harnessing them, we can increase our ability to observe, quantify and manipulate the
629 phenotypes of interest to EEID, as well as promote vertical integration of infection biology, as a
630 whole.
631
632 There is work to do in systems where hosts can recover from infections too, specifically in the
633 area of chronic infections. Of those infections where hosts can recover, low level chronic
634 infections of multiple weeks to years can develop in at least some animals (Hawley et al. 2005;
635 Achtman et al. 2007; Sakala et al. 2015). Yet we recovered few studies in which these chronic
636 infection dynamics were the subject of study, despite the fact that chronic infections can make
637 substantial contributions to the maintenance of disease in an epidemic context and alter the
638 measured shape of virulence-transmission relationships. No doubt, the rarity of chronic infection
639 studies is because, by definition, they take time. We must be careful not to take shortcuts
640 however, as our cousins the immunologists learned, when attempts to accelerate the
641 development of chronic infections by using larger pathogen inoculum than was normal led to a

642 qualitatively different immune responses and so defeated the whole exercise (Vidlak and Kielian
643 2016).
644
645 While studying only the immunological phenomena that are easy to observe could skew our
646 understanding of the ecology and evolution of infectious diseases, omitting rare events is also
647 an important gap. In his *Evolutionary Biology of Parasites*, Price noted 'The ecology of rare
648 events, an important aspect of life for parasites, is yet to be developed' (Price 1980). One such
649 rare event of importance in EEID is host range shifts, whose rarity as a subject of study among
650 the studies we reviewed, indicates that Price's statement may still be true. The rare nature of
651 host shifts makes them impossible to observe (at least in an unbiased way) in nature and thus
652 they *must* be the object of model systems research. Some models will be better than others for
653 studying rare events like host shifts and other rare events, such as the addition/loss of host
654 species as hosts or of transmission modes. We should prioritize systems where particularly vast
655 sample sizes can be generated e.g. (Longdon et al. 2011, 2015) and where the pathogen can
656 be safely contained (see discussions related to 'gain of function' experiments (Duprex et al.
657 2015)).
658
659 *Toward 'Horizontal Integration' or the comparative study of EEID*
660 While our review was not designed to uncover comparative research, it is clear from reading the
661 studies that we often do not perform research with a comparative mindset or with reference to
662 an infrastructure that would facilitate such an approach to research.
663
664 Yet comparative studies could help us draw general lessons about the ecology and evolution of
665 infectious diseases, as a number of recent studies have demonstrated (Leggett et al. 2012;
666 Acevedo et al. 2019), and our review shows that there is ample room to use experimental data
667 in this manner, at least as regards questions of (the interactions between) individual level

disease processes (Fig. 3a). The systems reviewed herein share several features, merely by dint of being experimental systems used for EEID research. In all systems, infections can be generated, a metric of disease measured, and pathogens enumerated. In almost all systems, moreover, 'individual' level variables such as host strain, parasite strain, and parasite inoculum could be (or have been) simultaneously varied. As such, we are well-placed to ask key questions in EEID from a comparative perspective — e.g., are there thresholds for the establishment of infection and disease? How does pathogen burden vary with disease through time? Does disease predict transmission? To systematically use model systems in this way, however, we first need i) standardized experimental protocols, and ii) the infrastructure for sharing/storing the data generated. Examples of large-scale efforts to conduct similar, ecological experiments exist (e.g., the NSF Research Coordination Network, Nutrient Network) and could serve as a blueprint for such an effort in EEID.

The project of designing standard experiments should be performed with reference to theory (e.g., (Day 2002)) and may itself stimulate theoretical research. Take the example of dose-response experiments, which are routinely conducted as part of system optimization but can also illuminate host-parasite interactions within-host. Should inoculum size be varied by a consistent scale (arithmetically, logarithmically) across systems and how should this change with pathogen type (e.g., bacteria vs. helminths, or macro vs. microparasite)? As of now, parasite inoculum is commonly varied logarithmically but there are other possibilities – e.g., might we consider varying dose with reference to relative biomass or metabolic rate, in the interests of understanding the energetic requirements of maintaining an infection? Theory can also help us with the prospective interpretation of data that has already been collected. To stay with the dose-response example, many dose-response experiments already exist (P.A. Clay and M.A. Duffy, unpublished manuscript) and there are likely many others that went unpublished. By illuminating how our inferences about disease processes are affected by study

694 design, theory can enable these older datasets to be used to their fullest. Theory also has a key
695 role in providing precise definitions of key terms, without which we cannot hope to make
696 comparisons between studies. Our review suggests common definitions are greatly needed
697 since there was great variation in the way even the most commonly invoked and important
698 concepts in EEID were defined. For example, in the papers we reviewed, virulence was defined
699 in the same way that we have used it here, as well as to mean the harm an infection causes to
700 the host (without respect to 'who' caused it), the capacity for a parasite to infect a host (Flor
701 1958; Barrett et al. 2007), and the capacity for a parasite to kill a host (Fenner 1949*c*).
702
703 In addition to standardized experimental protocols, an infrastructure for the collation, storage,
704 and sharing of data generated is required if we are to use comparative analyses of experimental
705 data to uncover general rules underlying disease processes. There is already a successful
706 example of a data-sharing bank in EEID (Stephens et al. 2017) but few resource-sharing banks.
707 In genetics, strain banks enable researchers to order specific strains of an organism, which
708 allows them to replicate experiments already conducted or build upon them. In some of the
709 pathosystems reviewed, particularly those with roles in the biomedical sciences (e.g., *P.*
710 *chabaudi* or *H. polygyrus*), pathogen and host strains are available via public banks. In others,
711 however, pathogen 'isolates' – which likely contain myriad pathogen genotypes – are used to
712 generate infections and/or pathogen/hosts are sourced directly from the field. This lack of
713 standardization is sometimes essential for pursuing the question at hand. In such cases, the
714 collection and storage of excess source material could enable posthoc strain
715 development/maintenance for comparative work (though this will sometimes be logistically
716 impossible). Small as the field of EEID currently is, an *ad hoc* system for sharing data and
717 resources may suffice for now but, going forward, establishing protocols for the sharing of data
718 and resources will help us to replicate experiments, widen and democratize access to research

719 resources, and, most relevant to the theme of this paper, generate general insights about
720 disease processes.
721
722 **Part III: Developing criteria for model systems in EEID**
723 In parts I and II we used a concept of model systems borrowed from the biomolecular sciences
724 as a reference point for a discussion of what ecologists and evolutionary biologists of infectious
725 disease use 'model systems' for and how they might use them better. But EEID has a different
726 outlook and different priorities the cellular-molecular-developmental fields of biology. Right off
727 the bat, it was clear that this biomolecular conception of model systems was not a perfect fit.
728 Model organisms in genetics, for example, are 'not primarily studied because they are
729 interesting in their own right' (Ankeny and Leonelli 2011). By contrast, many of the model
730 systems in EEID were established and are studied precisely because they are fascinating
731 examples of evolution's mischief or because they are of medical, agricultural, or conservation
732 concern. As such, experimental systems in EEID serve *both* as interesting foci and are used to
733 elucidate general rules about infectious diseases. This illustrates that EEID as a field may want
734 to establish a bespoke definition of what a model system is and what it can be used for. In this
735 part of the paper, we highlight issues that other fields have had to confront in their discussions
736 about model systems, as a jumping off point for our own.
737
738 The essential idea that underpins model systems research is that we can learn about the basic,
739 general principles of nature from organisms that have features that make them well suited to
740 research, because these model organisms share key features with other, less-easily studied
741 organisms (Krebs 1975). That is to say, model organisms are *representative* of other organisms.
742 Holmes traces this idea to Aristotle's observation that different organisms share consistent body
743 plans (Holmes 1993) and, of course, we now know that such similar traits are often (though not
744 always) the result of evolutionary conservatism (Jenner and Wills 2007).

As we think about the design and use of model systems in EEID, then, we must ask ourselves at what level of biological organization do diseases have the equivalent of a similar 'body plan'? Is phylogenetic relatedness what unites pathosystems and, if so, across what level of taxonomy can we generalize i.e. can one virus only be a useful model of viruses in its family or of viruses in general? Assessing the representativeness of model systems based on their taxonomy alone seems too limited. After all, the models developed from IEV and measles have been expanded to explain the dynamics of, e.g., bacterial infections like pertussis. It seems more important that our model systems represent the characters or key concepts of interest to our field (Travis 2006; Jenner and Wills 2007), an idea implicit in the theory-first way we that conducted this review. The work of Anderson & May suggests that systems might be usefully grouped for comparative purposes into the categories of microparasite vs. macroparasite (Anderson and May 1991). Indeed, in performing this review, it felt 'unnatural' to lump together the replication of microparasites and maturation of macroparasites into one category (Table 2), since these processes involve different energetic requirements on the part of host and parasite, stimulate different sorts of immune defenses, and thus very likely have different evolutionary consequences. An alternative way to group pathosystems might be at the level of parasite life cycle: e.g., complex vs. simple, obligate- vs. non-obligate killer, which can greatly impact ecological and evolutionary dynamics (O'Keefe and Antonovics 2002). Importantly, it may not be enough to consider the traits of just parasites. EEID, unlike anatomy, genetics, or evolutionary developmental biology, requires model systems that represent the *relationship* between two organisms. We may thus need to pay attention to or define metrics that measure the interaction between pathogen and host — e.g., a measure of the *relative* speed of pathogen and host evolutionary rates, to elucidate which systems are representative of one another.

770 Much of the recent debate about the representativeness of model systems has focused on the
771 extent to which the traits that make models easy to study also make them unrepresentative of
772 organisms at large, and so bias the picture they give us of the natural world (Alfred and Baldwin
773 2015). For example, in his classic paper on what makes a model system, Krebs noted that one
774 thing that makes model systems useful is the 'magnitude of the phenomenon to be studied' —
775 i.e., that the model systems possess the trait of interest in abundance (Krebs 1975). Recently it
776 has been argued that organisms possessing extreme characters may be very derived,
777 originating in relatively unusual unconstrained ecological and evolutionary contexts, and so are
778 ill representative of (the processes that generate) biodiversity at large (Alfred and Baldwin
779 2015). This idea has driven a push toward extending the taxonomic sampling in genetics and
780 other fields.
781
782 The extent to which the model systems reviewed here are biased, and the biases generated by
783 any future-defined selection criteria for model systems, deserves debate. Ironically, the lack of a
784 well-defined notion of a model system may have spared EEID some of the problems that arise
785 due to the biased sampling of systems in other fields whereby they only exhibit the very
786 extremes in the traits of interest or a specific taxonomic group. The majority of systems
787 reviewed here were first studied either in another disease-focused field, like parasitology or
788 immunology, as models of a specific disease, and/or because of their applied importance (Table
789 1). Thus, while they are united in being pathogenic, they represent a relatively random
790 taxonomic set and, unlike many infections studied in the biomedical sciences, do not represent
791 the most pathogenic of diseases. This set of pathosystems may not represent infectious
792 diseases in other ways, however, most obviously because traits that make them easy to study in
793 the laboratory may not be widely distributed in nature. For example, as we have noted, in many
794 of the systems reviewed the (most commonly studied) host cannot recover. This feature makes
795 these pathosystems easy to study - they can be modelled using a simple SI framework and, in

796 the context of laboratory studies of epidemics, reduce the time required for sampling, since
797 researchers only need to track individuals until infection is confirmed.
798
799 Are these systems thus unrepresentative of the many infections that do resolve? In some ways,
800 certainly. But that does not mean they entirely uninformative about the process of recovery.
801 Take an analogy from evolutionary developmental biology. Jenner & Wills countered the
802 argument that systems invulnerable to environmental change were poorly placed for
803 understanding environmental influence on development (Jenner and Wills 2007), by noting that
804 such systems could help evolutionary developmental biologists understand the complementary
805 phenomenon of canalization. In a similar vein, non-resolving diseases might help illuminate
806 much about tolerance, a host response complementary to, and which coexists alongside,
807 resistance.
808
809 Indeed, it might be argued that the ways in which model systems fail to represent other systems
810 are just as, if not more, useful than the ways in which they are. Take the example of *M. lini* and
811 *P. ramosa*. Interactions of these two pathogens and their hosts are mediated by 'matching'
812 interactions between their genes and that of their hosts. These systems are often used by EEID
813 researchers to ask similar questions, for example the impact of space and metapopulations on
814 disease dynamics. Yet, their coevolutionary dynamics are different because of the details of
815 what happens when a parasite and host genes 'match' (mediating 'incompatibility' and
816 'compatibility', respectively) (Thrall et al. 2016). So, details matter, and teach us where our
817 theory falls down and motivate us to make it anew. This fact is not at odds with the program of
818 model systems research, however, for we cannot understand whether the details are consistent
819 with, or contrary to, theory if we do not set out to do research in a comparative context.
820
821

Conclusion

As a relatively young field, EEID nonetheless has a number of systems that are used as touchstones. While the earliest systems were laboratory-based and borrowed from other fields, with time we have developed our own. These newer systems, which often incorporate the field and lab, give us access to greater variation in hosts and parasites and permit the exploration of processes at different scales. Yet success has been variable. Laboratory models have been used with limited success to address foundational questions about the effect of parasites on population or ecosystem level processes and vice versa. A concerted effort toward vertical integration within systems would address this gap. Similarly, systematic horizontal integration between systems could help us to establish whether phenomena observed in one system can be generalized to others and to elucidate general rules underlying disease transmission. Indeed, as we have learned during the writing of this piece, the very exercise of asking 'what do we want from our model systems?' can help establish concrete, consensus definitions of concepts or experimental designs that could be used across the model systems in EEID.

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Author contributions

NW conceived of the framing of the paper, performed the literature review, and wrote the paper. MAD provided feedback on the framing of the paper and edited the manuscript.

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Box 1: Key questions in EEID

EEID is a diverse field with roots in parasitology, immunology, epidemiology, and population biology in addition to ecology and evolutionary biology. It is no surprise, then, that the questions of interest are diverse. Here we outline some of the major themes of interest to EEID researchers.

Parasites as drivers of host population abundance, dynamics, and diversity (& vice versa)

'(How) do parasites maintain genetic diversity in host populations?' and '(how) do parasites control host population abundance?' are two of the oldest questions in the field, the subject of papers that act as touchstones in the field and a continued subject of debate and research (Lively et al. 2014; Brandell et al. 2020). There has been longstanding interest in the reciprocal processes — how host population abundance and diversity impact the evolution of parasite traits, in particular virulence and transmissibility, and the coevolutionary dynamics that can thence ensue. Indeed, coevolutionary interactions have been of interest throughout EEID's short history. Community level processes that could impact the probability of a parasite moving between hosts are a particularly active area of interest. In particular, the concept of the dilution effect, which states that host biodiversity at the community level can reduce the risk of disease in a particular host, is an ever-growing area of research (Keesing et al. 2010; Rohr et al. 2020).

The impact of the environment external to the host on disease

There is increasing interest in how ecological interactions, other than those between host and parasite, alter disease transmission and host-parasite (co)evolution (Lively et al. 2014). Perhaps motivated by the pressing challenge of climate change and the prevalence of studies of vectorborne diseases in EEID (Brandell et al. 2020), the impact of temperature on disease dynamics has received considerable attention (Lafferty 2009; Mordecai et al. 2017). The effect

of additional abiotic factors, including host diet and habitat structure, are also areas of active research (Hite et al. 2019). In addition to these abiotic factors, the role of predators in altering disease transmission, via their impact on host population density as well as through indirect effects, has been the subject of both theoretical and empirical research (Choo et al. 2003; Packer et al. 2003; Duffy et al. 2019). A notable recent trend is to understand how hosts select and use their habitats to avoid infection and how parasites, in turn, manipulate their hosts to promote their transmission (Hughes 2013; Weinstein et al. 2018).

The drivers of disease emergence

As infectious diseases emerge at an increasing rate (and at the time of writing, threaten our lives and livelihoods) (Jones et al. 2008), ecologists and evolutionary biologists have sought to understand the factors that drive their emergence. Emerging infectious diseases often spillover from animal reservoirs and, as a result, the ecological and evolutionary factors that enable parasites to 'jump' hosts and thence establish in a host population have received much attention (Lloyd-Smith et al. 2009; Babayan et al. 2018).

Within-host interactions

The impact of within-host interactions, whether that be between parasite strains/species or between parasites, hosts, and the microbiota, on disease dynamics is an active area of research that has perhaps the greatest overlap with the immunological and parasitological fields in which EEID is rooted. Studies of pathogen-pathogen interactions are conducted both to understand the eco-epidemiological dynamics of infectious diseases (e.g., how does a coinfection alter the spread of a focal pathogen? (Marchetto and Power 2018; Clay et al. 2019)) as well as to understand the evolution of parasite traits including virulence, transmissibility, and drug resistance (deRoode et al. 2005; Birger et al. 2015; Wale et al. 2017). Studies of the microbiota meanwhile focus on the microbiota as a unit (e.g., using antibiotics to ask 'how does

1394 the presence of microbiota alter host and pathogen fitness'), as well as its community ecology
1395 (e.g., 'how does the microbiota assemble?' 'How is it affected by pathogens & host genotype
1396 (and vice versa)?' And, 'are some species more important than others'?) (Gonzalez et al. 2011;
1397 Koskella et al. 2017). Here, EEID overlaps with the wider field of microbial ecology. Within-host
1398 studies are often characterized by a focus on the on the dynamical nature of microbial
1399 populations; a major challenge in EEID is to understand how these dynamics translate to
1400 epidemic dynamics (Mideo et al. 2011; Clay et al. 2019).
1401

Table 1: **Experimental systems included in the literature review herein.**
Superscripts indicate [1]first and [2]second intermediate hosts, *definitive host.
Pathogen classifications follow those of Schmid-Hempel (2011).

Pathogen name(s)	**Pathogen classification**	**Host classification**	**'Founding' EEID researcher(s)** (decade of first publications)	**Field of origin** (% of 10 most cited experimental papers from EEID)	**Life cycle & transmission mode**	**Can life cycle be completed in lab?**	**Recovery Occurs?**
Melampsora lini	Microparasite, fungus	Plants	**Henry Flor** (1930s), Jeremy Burdon (1980s)	agriculture, genetics, (60%)	Direct; wind-borne	Yes	No, within a season (Ravensdalle et al. 2011)
Infectious ectromelia virus	Microparasite, virus	Rodent	**Frank Fenner** (1940s)	Medicine (smallpox model),EEID (0%)	Direct; physical contact, fomites	Yes	Yes (Chaudhri et al. 2004)
Hymenolepis diminuta or *Taenia taenia*	Macroparasite, cestode	Insects[1] Rodent*	**Marietta Voge** (1950s), Clark Read, John Holmes	EEID (50%)	Indirect, obligate multi-host	No	No in rat; yes in mouse (Read 1967; Chappell and Pike 1976).
Heligmosomoides polygyrus or *Nematosporoides dubius*	Macroparasite, nematode	Mammals (rodents)	**Clark Dobson** (1960s), Anne Keymer	medicine, parasitology (10%)	Direct; ingestion of larvae.	Yes,	Yes (Reynolds et al. 2012)
Diplostomum spathaceum	Macroparasite, trematode	Molluscs[1] Fish[2]	**John Stables** Leslie Chappell (1990s), E. Tellervo Valtonen	fisheries, parasitology (100%)	Indirect, obligate multi-host	No. 1st & 2nd intermediate host studied	No (Whyte et al. 1990)
Crithidia bombi	Microparasite, protozoa	Arthropods (bumblees)	**Paul Schmid-Hempel** (1990s)	EEID (100%)	Direct; fecal-oral	Yes	Rarely (B. Sadd, *personal communication)*
Pasteuria ramosa	Microparasite, bacterium	Zooplankton	**Dieter Ebert** (1990s)	EEID (100%)	Direct; ingestion spores in water.	Yes	Rarely (Hall and Ebert 2012)
Plasmodium chabaudi	Macroparasite, protozoan	Rodents[1] Arthropods*	**Andrew Read** (1990s)	Medicine (malaria model), parasitology (30%)	Indirect, vector-borne.	Yes, rarely.	Yes (Stevenson et al. 1982)
Mycoplasma gallisepticum	Microparasite, bacterium	Birds*	**Andre Dhondt** (1990s)	agriculture/ conservation (60%+)	Direct.	Yes	Yes (Kollias et al. 2004)
Ribeiroia ondatrae	Macroparasite, trematode	Molluscs[1] Amphibians[2], Birds*	**Pieter Johnson** (1990s)	EEID/ conservation (100%)	Indirect, obligate multi-host	No. 1st & 2nd intermediate host studied	Varies with host (Johnson et al. 2004)

Table 2: **Definitions of categories to which studies were allotted.** Each study can be allotted to multiple categories.

phenomenon	organism	trait	definition
transmission	pathogen	infectivity	Capacity to successfully enter the host.
		replication	Capacity to grow in population size *or* grow/mature inside the host.
		dispersal capacity	Capacity to leave the host e.g. no. of transmission stages.
		entry to exit	Capacity to enter the host, replicate and be ready to transmit.
		realized transmission	Capacity to enter, replicate and exit a host and find a second.
	host	susceptibility	Readiness with which host becomes infected
disease	pathogen	virulence	Contribution of parasites to host disease.
	host	tolerance	Capacity for host to maintain health when bearing a given burden of parasites.
		resistance	Capacity to kill parasites.

Table 3: **Definitions of scales to which variables were allotted.** Each variable within a study can be allotted to multiple categories.

Scale	trait	examples
within-host	Pertains to variation generated at, or processes that occur, within the host	*dynamics* of host or parasite cell types, presence or absence or number of co-infecting species or strains, tissue tropism, movement within host
individual	Pertains to a characteristic of an individual host or parasite or a host or parasite strain	genetics, behavior, sex, age, frequency, color, motility **host only**: immune status, maternal immune status **parasite only**: inoculum size,
ex-host	Abiotic aspect of the host environment that is proximate to the host individual	diet, light conditions, pH conditions, medication
population	Pertains to factors that vary at a population level. Can be generated due to temporal variation within a population or spatial variation among populations.	demography, age structure, social structure, genetic diversity.
community	Pertains to organisms other than the host or parasite or characteristics that define their interactions with them.	host diversity, predator presence or absence, antipredator behavior, host community composition, host range
ecosystem	Pertains to ecosystem scale processes and the measure that define them	chemical composition, biomass, nutrient cycling

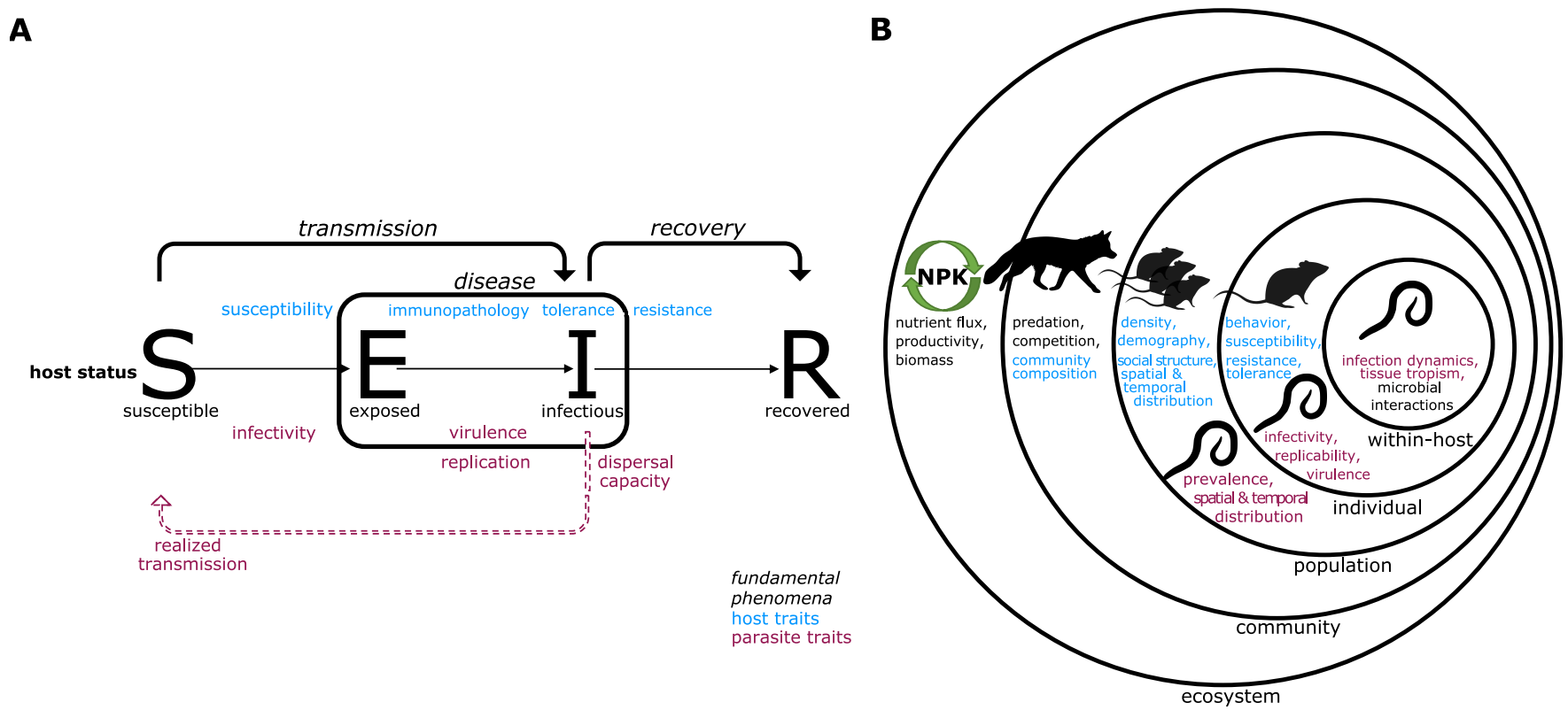

Figure 1: The phenomena of interest to ecologists & evolutionary biologists of infectious diseases & the scales of biological organization at which they occur. A. Epidemiological models define the central processes of importance to the ecology and evolution of infectious diseases. Individual hosts transition between epidemiologically distinct states (black): susceptible, exposed, infectious and recovered. Hosts transition between susceptible and infectious states via the process of transmission and exit via the process of recovery (or death, not shown). Both parasite (pink) & host (blue) traits are involved in the key phenomena (italics). On the part of the parasite, transmission is governed by infectivity (the parasite's capacity to successfully enter and establish within a host), replication (here defined, for simplicity, as the process by which parasites either replicate or mature within the host) and dispersal capacity, the ability to successfully exit the host. For the purposes of this review, when the entire cycle is completed and the parasite successfully enters a host, replicates, exits and makes it to a new host, we say that transmission is 'realized'. The host, of course, also determines parasite transmission: host susceptibility mediates the probability that a parasite successfully infects the host and the host can cause parasite mortality (our narrow definition of resistance). Infections cause disease (black box), to which both parasite and host may contribute, via virulence and immunopathology alike. Immunopathology and parasite virulence can be alleviated by host tolerance. Infectious hosts may exit the diseased state via the process of recovery, as mediated by resistance, medications or death (not shown). The host and parasite traits involved in these phenomena may (co)evolve and are thus the focus of evolutionary studies of infectious diseases. Note that, in the case of multi-host parasites, each may trait may vary with the identity of the host. **B.** Infectious diseases impact, and are affected by, processes at multiple ecological scales. Parasite and host ecology and behavior can impact parasite (pink) and host (blue) traits and populations, and vice versa. In addition, other phenomena (black) at the within-host, population, community and ecosystem scales can impact parasite/host population dynamics and evolution, and vice versa. The challenge of model systems research is to investigate, and ideally quantify, the importance of these interactions for parasite ecology and evolution.

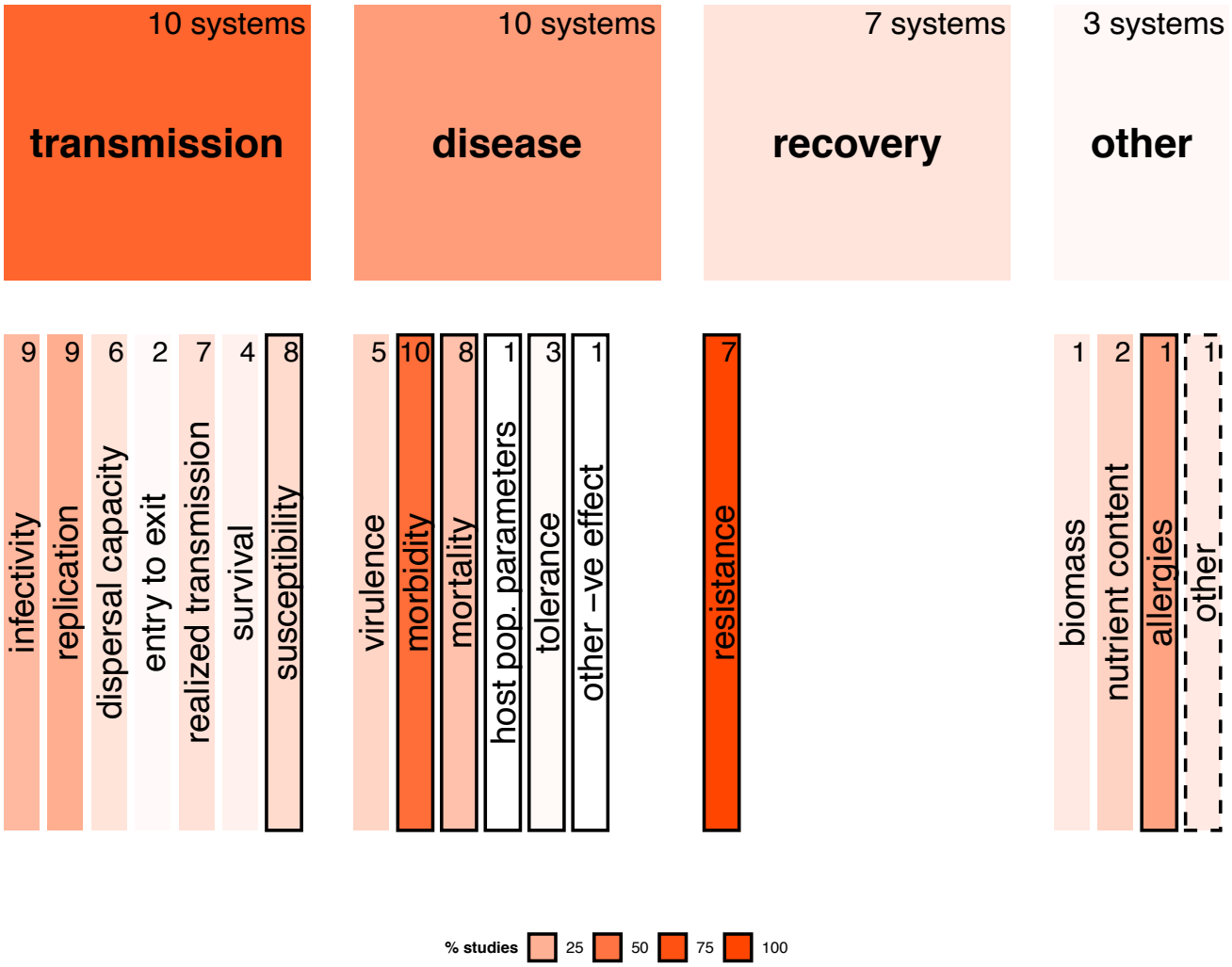

Figure 2: The extent that model systems in EEID are used to investigate the key phenomena of interest to the field. Top row: the shade of the square indicates the proportion of studies reviewed in which in the phenomenon is studied in our review. The number of study systems, of the 10 total, in which this phenomenon is the focus of study in at least once is indicated in the top right of the square. Bottom row: Each rectangle represents the trait or process indicated. Shading indicates the proportion of studies, which fall under the umbrella phenomenon, that focus on that trait/process e.g. 'morbidity' is bright orange, indicating that a large proportion of studies *of disease* focus on morbidity. Rectangle borders indicate whether the trait is a feature of the parasite (no border), host (solid) trait or neither (dashed). The numbers at the top of each rectangle indicate the number of study systems (of a total of 10) in which the focal trait is the focus of at least one study. Note that a single study can be allotted to more than one category.

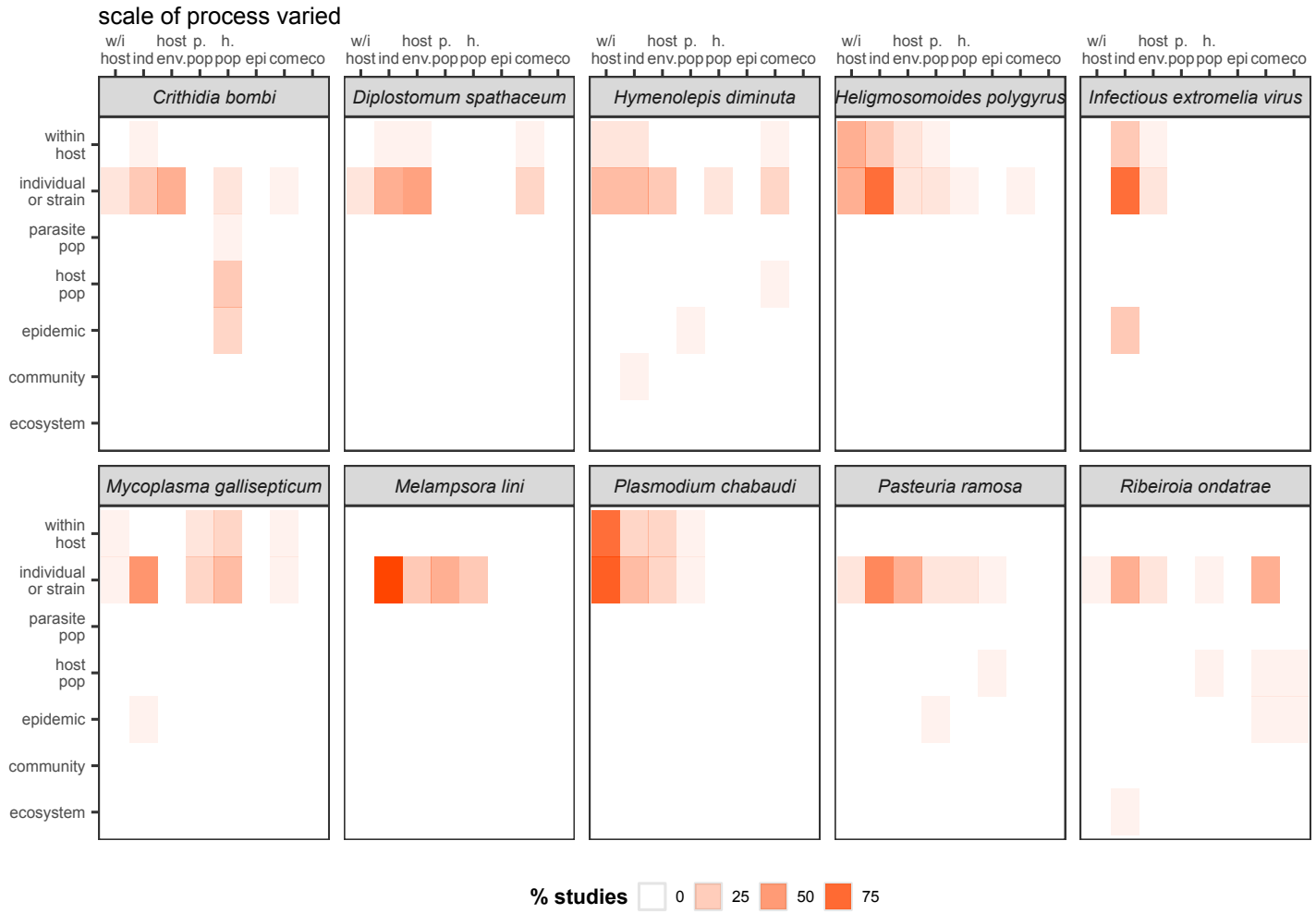

Figure 3: Model systems research tends to focus only on the small-scale ecological interactions that influence disease dynamics and there is limited vertical integration within model systems. Each panel corresponds to one of the 10 systems reviewed. The scale of independent variables is indicated on the top of each panel, the scale of dependent variables on the left of each panel (see Table 3 for information on which experimental variables are allotted to each scale). White space indicates that we found no studies that focused on the interaction of processes at the corresponding scales in our review; shaded areas indicate that there was at least one there was at least. The intensity of shading indicates the proportion of studies in a certain system that fell into the corresponding category.