The Use and Underuse of Model Systems in Infectious Disease Ecology and 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 the term "model systems" and what they want from them is unclear. This uncertainty hinders 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 10 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 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. Furthermore, studies tend to focus on only a few 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.

Keywords: model system, disease ecology and evolution, ecology and evolution of infectious diseases (EEID), multiscale, within host, ecosystem.

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 the term "model system" is far from clear. The phrase is invoked variously to mean that a particular experimental system is tractable (i.e., the host and/or parasite has a fast generation time, is easily culturable, and/or is easily manipulated; Antonovics et al. 2002; Ebert 2008; Koch and Schmid-Hempel 2011), is a model of a specific disease (Buckling et al. 1997), or is 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 about the conception and utility of model systems in the study of infectious disease ecology and evolution.

The use, definition, and design of model systems is a matter of 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 organism is achieved (although in actuality the ecology and evolution of model organisms used in cellular, molecular, and developmental biology is rarely studied; Alfred and Baldwin 2015). Last, 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, and developmental perspective echo the statement of Joseph Travis, in his presidential address to the American Society of Naturalists: "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, p. 307).

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 them 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—that is, whether these gaps actually represent underuse of systems. Last, 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).

Both pathogen (fig. 1A, italic text, dark gray) and host (fig. 1A, roman text, light gray) traits influence transmission, disease, and recovery. 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). Last, 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 or expel pathogens (rather than as the opposite of susceptibility, as it is sometimes defined; e.g., Thrall and Burdon 2003).

The parasite and host traits that govern transmission, disease, and recovery can vary between individuals, be heritable, and have significant fitness effects; thus, these traits can and do evolve in response to selection. Both parasite and host traits are subject to selection from ecological factors, such as abiotic or biotic stressors (e.g., predators); moreover, host phenotype exerts selection on parasite traits and vice versa. 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 presence and strength of trade-offs between the traits that govern the different phenomena influence the trajectory of trait evolution. 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 among within-host replication, virulence, and dispersal capacity. Similarly, trade-offs between host resistance and tolerance can influence the evolution of these traits (Raberg et al. 2007) and, ultimately, the amount disease associated with a particular infection.

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, we were unable to isolate which of the transmission traits were being studied and/or multiple traits were being assessed. For example, in a study of epidemic dynamics, the focus is not on parasite replication, infectivity, or dispersal capacity but rather on

Table 1: Experimental systems included in the literature review herein

Pathogen name(s)	Pathogen classification	Host classification	Founding EEID researcher(s) (decade of first publications)	Field of origin (% of 10 most cited experimental articles from EEID)	Life cycle and 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	Rodents	**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] rodents[*]	**Marietta Voge** (1950s), Clark Read, John Holmes	EEID (50)	Indirect, obligate multihost	Yes	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 multihost	No (first and second intermediate host studied)	No (Whyte et al. 1990)
Crithidia bombi	Microparasite, protozoa	Arthropods (bumblebees)	**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 multihost	No (first and second intermediate host studied)	Varies with host (Johnson et al. 2004)

Note: Superscripts 1 and 2 indicate, respectively, the first and second intermediate hosts; asterisks indicate the definitive host. Pathogen classifications follow those of Schmid-Hempel (2011). Boldface type indicates the founding researcher. EEID = ecology and evolution of infectious diseases.
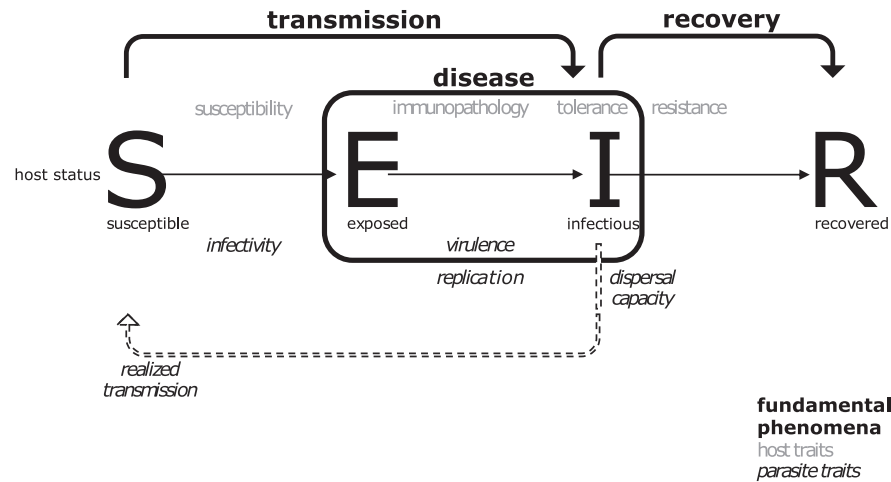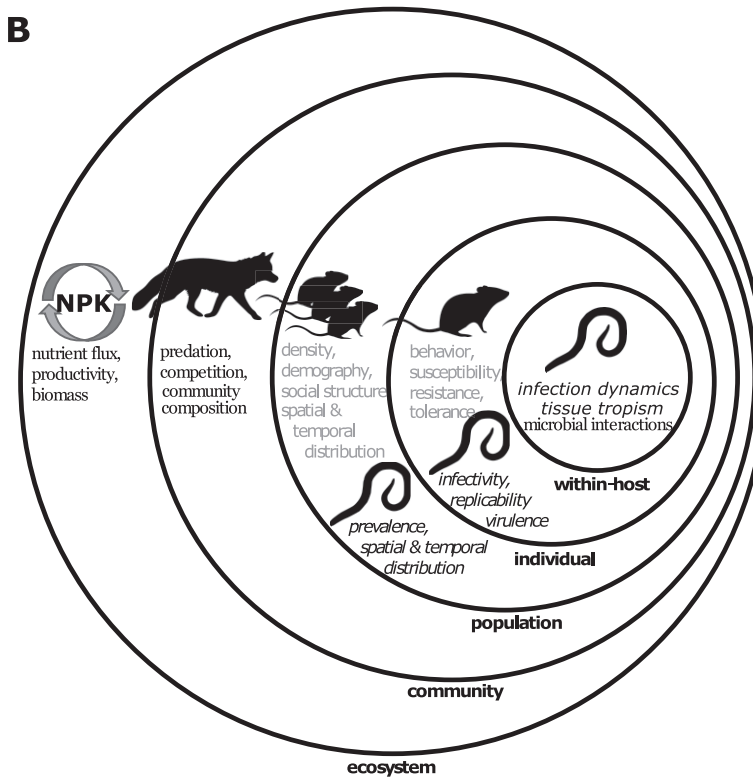
Figure 1: The phenomena of interest to ecologists and evolutionary biologists of infectious diseases and the scales of biological organization at which they occur. *A*, Epidemiological models define the central processes of importance to the ecology and evolution of infectious diseases. Individual hosts transition between epidemiologically distinct states: 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 (italic text, dark gray) and host (roman text, light gray) traits are involved in the key phenomena (boldface text). 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 as the process by which parasites either replicate or mature within the host, for simplicity), 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 multihost parasites, each trait may vary with the identity of the host. *B*, Infectious diseases impact and are impacted by processes at multiple ecological scales (boldface text). Parasite and host ecology and behavior can impact parasite (italic text, dark gray) and host (roman text, light gray) traits and populations and vice versa. In addition, other factors, such as interspecies interactions at the within-host and community scales and ecosystem-level processes (alternate font), 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 and host ecology and evolution. A color version of this figure is available online.

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—that is, 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 which manifestation(s) of disease (morbidity, mortality, etc.) were being monitored. Last, 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 and how they were measured, and we were alert to trends in research methodologies.

Focal Questions in EEID and 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, and recovery

Table 2: Definitions of categories to which studies were allotted

Phenomenon, organism, trait	Definition
Transmission:	
Pathogen:	
Infectivity	Capacity to successfully enter the host
Replication	Capacity to grow in population size or to grow/mature inside the host
Dispersal capacity	Capacity to leave the host (e.g., number 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 or expel parasites

Note: Each study can be allotted to multiple categories.

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, infectious diseases can impact ecological interactions at a variety of scales (fig. 1*B*). Therefore, in addition to noting which of the key phenomena each study addressed, we also recorded the scale of the phenomenon or 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. Table 3 and figure 1*B* contain details on which experimental variables were assigned to which scale.

Systems Reviewed. We examined which of the key phenomena (i.e., transmission, disease, recovery) 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 invertebrates to mammals). To cover as great a breadth as possible, we set two criteria determining whether a system could be included. The first was that researchers had to have the ability to induce infection experimentally, since the capacity to manipulate the presence of infections seems to be a basal requirement for their experimental study. We did not require that the entire transmission cycle of the parasite could readily be completed in the laboratory since, as we discuss more in the "Population and epidemic level" section below, doing so would have severely restricted our ability to conduct this review. Second, the system had to be a focus of ecological or evolutionary study for greater than 10 years, since researchers cannot be expected to have established a holistic study system in less time than that. Beyond that, we endeavored to limit overlap between host or pathogen types.

By necessity, the list of systems (table 1), though broad, is not exhaustive. First, we omitted a number of important pathosystems where experimental inoculation of the host is possible but is used relatively rarely as an experimental methodology (at least among the studies recovered using our search criteria). This was the case for the snail-trematode system *Microphallus-Potamopyrgus*, for example, which has made an important contribution for our understanding of host-parasite coevolution (Dybdahl and Lively 1998; Lively and Dybdahl 2000; Morran et al. 2011). Second, we omitted bacteriophage-bacteria systems, although they permit experimental inoculation of hosts

Box 1: Key topics in the ecology and evolution of infectious diseases (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 (and Vice Versa)

The questions "(how) do parasites maintain genetic diversity in host populations?" and "(how) do parasites control host population abundance?" are two of the oldest in the field, the subject of articles 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 long-standing 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 vector-borne 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 effects 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 spill over 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 they be between parasite strains and species or among 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) and to understand the evolution of parasite traits, including virulence, transmissibility, and drug resistance (de Roode 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 the presence of microbiota alter host and pathogen fitness?) as well as its community ecology (e.g., how does the microbiota assemble? How is it affected by pathogens and host genotype (and vice versa)? And are some species more important than others? Gonzalez et al. 2011; Koskella et al. 2017). Here, EEID overlaps with the wider field of microbial ecology. Within-host studies are often characterized by a focus on the on the dynamical nature of microbial populations; a major challenge in EEID is to understand how these dynamics translate to epidemic dynamics (Mideo et al. 2011; Clay et al. 2019).

Table 3: Definitions of scales to which variables were allotted

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 coinfecting 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 as a result of 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 to 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 measures that define them	Chemical composition, biomass, nutrient cycling

Note: Each variable within a study can be allotted to multiple categories.

and have made a substantial contribution to our understanding of host and parasite (co)evolution and pathogen emergence (Horne 1970; Chao et al. 1977; Lenski and Levin 1985; Benmayor et al. 2009; Koskella 2014). Given the myriad host strain-phage combinations utilized in this subfield, this literature was unwieldy to review; it deserves a stand-alone review that can also address the specific biology of virus-bacteria interactions. In addition to systems where experimental inoculation is possible, there are several pathosystems where infections are not experimentally 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 *Heligmosomoides polygyrus* (Gregory et al. 1990; Knowles et al. 2013). We recognize that even within the inclusion criteria established above there are additional systems that could have been included (e.g., the stickleback-*Schistocephalus* system [Barber and Scharsack 2010], the *Silene-Ustilago* system [Alexander 1989]), but we nevertheless believe that the diverse systems that are included well reflect dominant research trends in EEID.

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 *H. polygyrus*, we also searched for *Nematospiroides dubius*. We identified the 10 most cited and five 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 distribution into the field or laboratory-based phenotypic assessment of field-collected material). We included least cited articles not only because they were likely to include the most recent research but also because personal experience has taught us that these articles 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 [IEV], and the rodent intestinal roundworm, *H. polygyrus*), the top 10 and bottom five cited articles did not address ecological and evolutionary questions. When this occurred, we performed an additional search to identify articles of an ecological or evolutionary nature by searching for "ecolog* OR evolution*" in the topic field in addition to the pathogen species name.

Last, to further capture older research, we identified one scientist who pioneered the study of each model system that we reviewed (in table 1, we list several researchers for completeness, but only the research of the boldfaced researcher was searched for). When fewer than five articles 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 articles by the founder in the final collection of articles for the system. In the case of IEV, 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 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 articles 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 when Anderson and May published their landmark articles 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 articles collated, we then extracted the following information from each article: (i) which of the umbrella phenomena (transmission, disease, recovery) was investigated, (ii) the variable(s) manipulated, (iii) the variable(s) measured, and (iv) the scale at which these variables were measured or manipulated (see "Focal Questions in EEID and 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.

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. 2).

Transmission. Transmission was the most studied phenomenon, being the focus of more than 80% of the 160 studies reviewed. However, the parasite traits involved in transmission (fig. 1*A*) were not equally represented (fig. 2). Infectivity and replication/development were well represented, being the focus of ~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 seven of 10 pathosystems, it was a regular focus of study (i.e., the focus of ≥20% of the articles) in only four systems: IEV, *Crithidia bombi*, *Diplostomum spathaceum*, and *Ribeiroia 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, *Melampsora 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 *Pasteuria ramosa*, which also coevolves with its host through the matching of genes that mediate infectivity/susceptibility (Thrall et al. 2016). Interestingly, our search did not uncover studies of recovery or resistance in *M. lini* and *P. ramosa*. This could imply that there is an evolutionary trade-off between defenses that block and clear infection (why invest in resistance if you do not get infected, after all?) or, recognizing that we reviewed only a subset of articles published in each system, this might reflect the relative degree to which different topics have been studied and/or cited. Indeed, we know that 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 host fitness, 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, fewer than half of the studies of disease focused on virulence and tolerance. Disease is a manifestation of the interaction of the host and parasite: here, we use the term "virulence" to denote the parasite's contribution to disease and the term "tolerance" to denote the amelioration of that effect by the host. Approximately a sixth of the studies of disease focused on virulence, and fewer than 5% focused on tolerance. Studies of virulence were conducted in five systems. Of these, genetic variation at the level of both the host and the parasite was
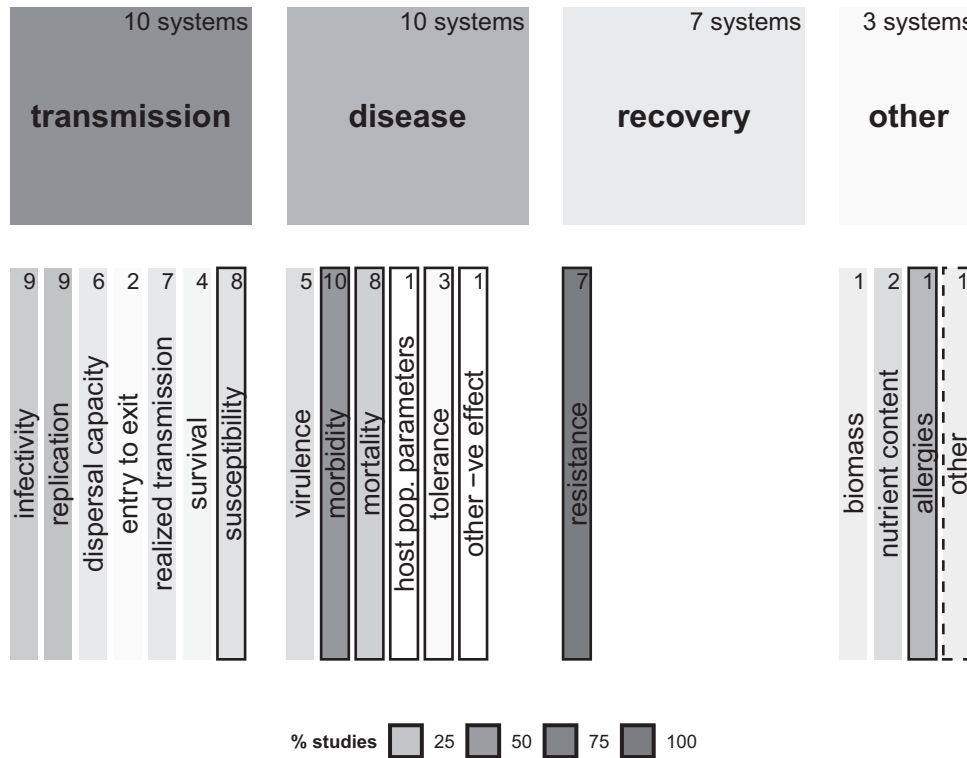
Figure 2: The extent to which model systems in the study of the ecology and evolution of infectious diseases are used to investigate the key phenomena of interest to the field. In the top row, the intensity of shading indicates the proportion of articles in which the indicated phenomenon was studied. The text at the top right indicates in how many of the 10 study systems the phenomenon was addressed at least once in the articles we reviewed. In the bottom row, each rectangle represents the trait or process indicated. The intensity of shading indicates the proportion of studies, which fall under the umbrella phenomenon, that focus on that trait/process (e.g., the morbidity box is nested under disease and is intensely shaded, indicating that a large proportion of studies of disease focus on morbidity). Borders indicate whether the trait is a feature of the parasite (no border), the host (solid), 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. A color version of this figure is available online.

exploitable for laboratory studies in two systems, *Mycoplasma gallisepticum* and *Plasmodium chabaudi*. This permitted the quantification of heritable variation in tolerance and virulence to disease in the same system, a necessary precursor for studying the coevolution of these traits (Little et al. 2010; although it is questionable how relevant that is in the *P. chabaudi* system, given that the host and parasite do not naturally co-occur). The majority of studies of disease did not focus on the contributions of host and parasite genetic variation to variation in disease severity. Rather, these studies focused on describing the symptoms of infection (e.g., Weimer et al. 1955; Goodman and Johnson 2011) or how they change with the host environment (Ferguson and Read 2002; Paull and Johnson 2011; Overholt et al. 2012).

Disease was measured using qualitative and quantitative measures of varying ecological and evolutionary signifi-

cance. In some systems, like *P. ramosa*—which is a castrating obligate killer of short-lived and rapidly reproducing zooplankton—the impact of infection on survival could be directly assessed (Ebert 2008). In others, disease was measured via quantitative health metrics such as cellular numbers, as in *P. chabaudi* (Taylor et al. 1998), or via a qualitative metric, as in *M. gallisepticum*, where the severity of conjunctivitis in birds was measured via an "eye score" (Kollias et al. 2004). In relatively long-lived animals, such as mice, fish, and birds, it is difficult to know how these measures translate into lifelong fitness (Graham et al. 2010), although our search did uncover studies where symptom severity was related to the likelihood that hosts were predated on (Seppälä et al. 2004, 2005). Furthermore, the effect of infection on behaviors directly related to fitness, such as mating (Kavaliers et al. 2003), foraging (Crowden and Broom 1980; Ponton et al. 2011; Adelman et al. 2015),

and predation (Webster et al. 1999), was assessed in a number of systems. Notably, in the studies we reviewed the effect of infection on hosts' susceptibility to predation was assessed only in systems where parasites are trophically transmitted (*D. spathaceum* and *Hymenolepis diminuta*), and as such these studies were as 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. In part, the paucity of studies in this category is likely to be a consequence of the fact that we assigned only a single trait, resistance, to it. We define resistance as the capacity for hosts to kill or eject parasites. Notably, hosts routinely clear parasites (and hence are able to "recover completely") in only four of the 10 study systems reviewed: IEV, *H. polygyrus*, *P. chabaudi*, and *M. gallisepticum* (table 1).

In the vast majority of 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*, the systems in which the host response can be manipulated (usually by preexposing hosts to the pathogen). It is likely that such "mechanistic" studies of resistance and recovery are possible in these systems because they involve vertebrate hosts whose immune system is relatively well characterized. Interestingly, although one of the oldest studies of *D. spathaceum* is mechanistic in nature (Stables and Chappell 1986*a*) and the system was established by parasitologists and 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, 2012); however, these studies were not included in the recovery category because they do not address inherent host resistance.

We shaped our review around an SIR framework, which was formulated to describe the dynamics of parasite transmission, and hence our discussion of recovery focuses on the extent to which hosts bear parasites (and so can transmit them). However, we recognize that other processes might be reasonably included in a discussion of recovery (e.g., tolerance or postinfection disease tissue repair). That

said, even had we included these processes in the category of recovery we might still have found that it receives little attention. Studies of tolerance were rare among those reviewed (see above), and we recall no studies in which hosts were followed up after infection.

At What Scales Are We Studying Key Phenomena? Approximately a third of the studies involve researchers looking at how "individual-level" factors—for example, parasite strain (Fenner 1949*a*; Rodriguez and Kleven 1980), host age (Fenner 1947*a*) or immune status, size of parasite inoculum (Fenner 1947*b*; Johnson et al. 2001; Karvonen et al. 2003), or inoculation method (Fenner 1947*b*; Lepak and Thatcher 1962)—impact individual-level variables. Since the majority of studies do not focus on interactions between individual-level processes, we focus on other scales from here on. We first address each scale in its capacity as a dependent and then an independent variable; some studies appear in multiple categories. To stimulate future research, we identify challenges involved in doing research at these different scales.

Within host. Within-host processes were either manipulated or measured in just over a third of the studies reviewed. The dynamics of parasite populations and their distribution within the host were the subject of the earliest articles that our review uncovered regarding *D. spathaceum* (Betterton 1974), IEV (Fenner 1947*a*), *H. diminuta* (Chandler 1939), and *H. polygyrus* (Dobson and Owen 1978). Within-host dynamics was the response variable in approximately a quarter of all studies reviewed. These addressed the way that within-host dynamics changed with parasite population parameters, such as initial size and genetic background, and with host factors, such as immunity, diet (Bansemir and Sukhdeo 1996; Ponton et al. 2011), and even temperature (Stables and Chappell 1986*a*).

A major theme of studies in the within-host processes category was interactions among parasites. 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, although 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 articles we reviewed focus on the interaction between parasites and the microbiota rather than parasite-parasite interactions (Koch and Schmid-Hempel 2011, 2012; Clerc et al. 2015; Zaiss et al. 2015). Interestingly, these articles often focused on the use of parasites to alter microbiota

to promote host fitness; in contrast, of the articles in our review that focused on parasite-parasite interactions, the predominant focus was on parasite fitness.

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 nondestructive repeated sampling of parasite and disease parameters (conjunctivitis and anemia, respectively) from single individuals was possible. This sampling methodology is made possible by the spatial distribution within the host of these pathogens, which fall at extreme ends on a gradient of tropism: *P. chabaudi* is distributed in the blood (at least during the stage of infection that is most often the subject of study), so one can sample the periphery without destroying the animal; *M. gallisepticum*, by contrast, is concentrated in and around the eye (although it can be found elsewhere; Dhondt et al. 2005).

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

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

Importantly, in several of the systems reviewed laboratory studies were conducted alongside studies of population- or epidemic-scale processes in the field. Such field studies facilitate the study of (co)evolutionary dynamics (Thrall et al. 2002; Ebert 2008; Bonneaud et al. 2018) that, in turn, further laboratory investigations. For example, approximately half of the studies of the effect of population variability on individual-level infection traits were conducted using *M. lini* and *M. gallisepticum*. In each of these systems, spatial dynamics of epidemics in the field drove parasite and host evolution that was then exploited to study the heritable variation in infectivity, virulence, and immunity in the laboratory (Thrall and Burdon 2003; Hawley et al. 2013; Bonneaud et al. 2019). *Pasteuria ramosa* provides similar opportunities to sample a diversity of pathogens and hosts as well as to analyze the effect of epidemics on host evolution (Duncan and Little 2007).

Community level. The relationship between interactions at the community level and the dynamics of infectious diseases comprised ~10% of the studies reviewed. With the growing importance of zoonotic diseases as a public and animal health problem, how parasites move between multiple hosts and why some hosts support pathogens but others do not have been the focus of much recent research (Johnson et al. 2012, 2019; Mollentze et al. 2014; Fenton et al. 2015; Olival et al. 2017). It was surprising, then, that only 6% of the studies reviewed examined variability among infections in different host species. The question of why some hosts are "better hosts" than others was specifically addressed in *H. diminuta* (Read and Voge 1954; Johnson et al. 2012) and *R. ondatrae* (Johnson et al. 2012); the former study was one of the oldest of all those reviewed. As an aside, the variation of infections among different host genotypes, which might be considered a topic analogous to host-species variation, was a focus of a further ~10% of studies reviewed (these were not counted as community-level studies). Of these, two studies distinguished themselves by using experimental evolution rather than standing trait variation to study host range (Dobson and Owen 1977; Brindley and Dobson 1981).

In addition to studies focused on the effect of host species identity on disease dynamics, further studies investigated how the community of hosts, specifically its composition, altered disease dynamics (Johnson et al. 2013, 2014). 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. (1998) investigated the impact of *H. diminuta* on interspecific competition between beetles. Other community-level studies focused on the interaction of parasites and predation (likelihood) in trophically transmitted systems (Seppälä et al. 2004; Orlofske et al. 2012).

There were a few studies that investigated how parasites withstand the ecological environment outside their host. Of these, two studies focused on the vulnerability of the parasite to predation (Morgan et al. 1997; Orlofske et al. 2012), while the remainder 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 rather than in parasites alone. Since the survival and reproduction of parasites outside the host can be a crucial determinant of parasite fitness and transmission, however, this area deserves attention.

Ecosystem level. Given the lack of studies conducted on the epidemiological level and the fact 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). Our review also uncovered another study of the chemical and nutritional analysis of parasites, which was conducted more than four decades before the latter and used the *H. diminuta* system (Roberts 1961). However, the results of this study—although eminently relevant to ecosystem processes—were interpreted in the context of their relevance to host-parasite interactions within the 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. Not only are disease dynamics influenced by ecological interactions that occur at multiple scales (within host, epidemic, etc.; fig. 1*B*), but interactions that occur at one scale may have a dramatic impact on those at another. However, our review suggests that the effect that processes at different scales have on one another is 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 of 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 or epidemic level, as discussed above, and the overall lack of work on infectious diseases at the ecosystem level (Preston et al. 2016).

Although 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). The consistent focus, across systems, on the (interactions between) small-scale processes suggests that there is significant potential for horizontal integration sensu Travis in this area.

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 so-called model systems are mere experimental systems—that is, they are used to investigate particular phenomena or processes as opposed to systems used to establish a holistic understanding of 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
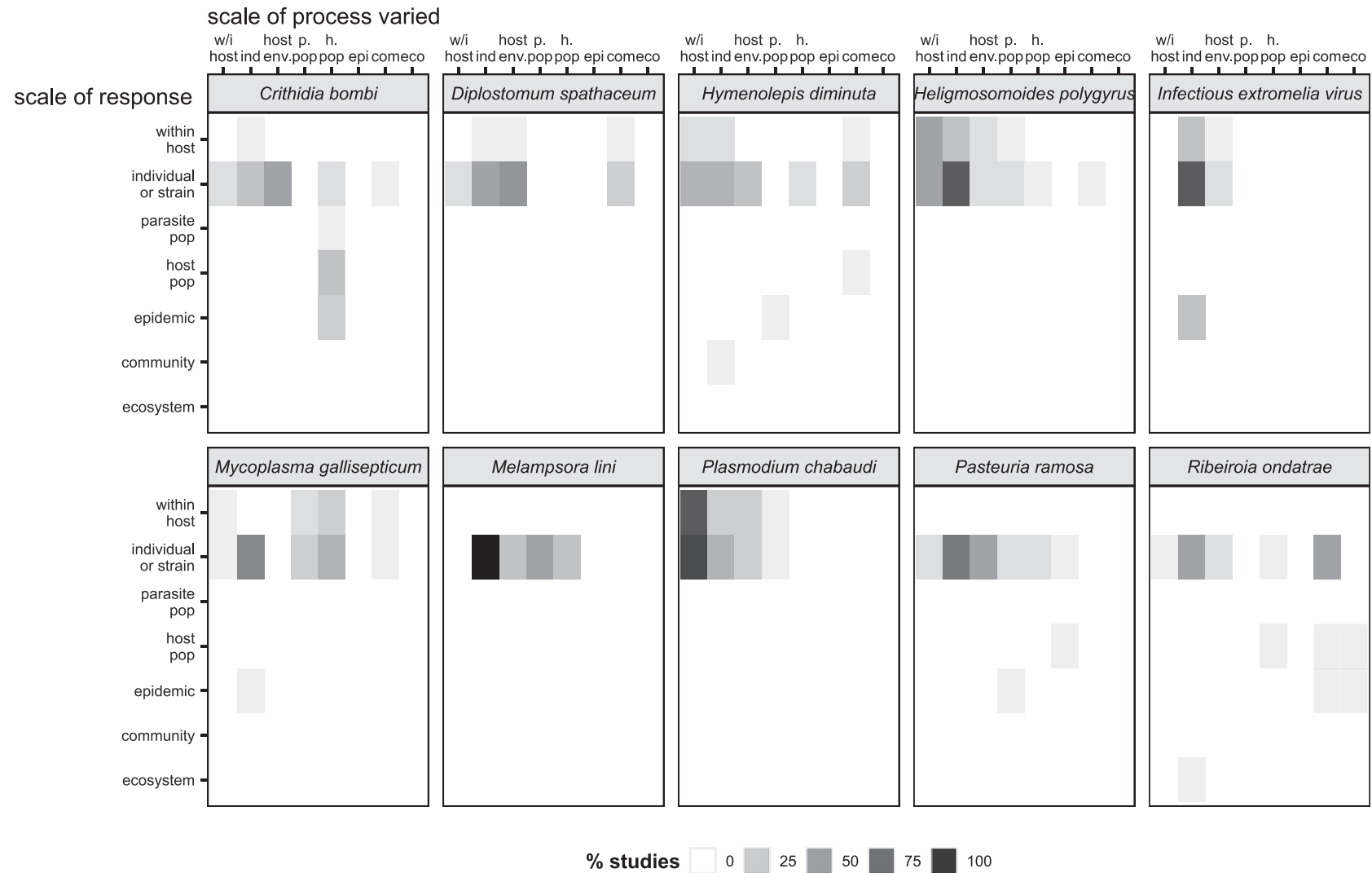
scale of process varied

scale of response

Crithidia bombi · *Diplostomum spathaceum* · *Hymenolepis diminuta* · *Heligmosomoides polygyrus* · *Infectious extromelia virus*

Mycoplasma gallisepticum · *Melampsora lini* · *Plasmodium chabaudi* · *Pasteuria ramosa* · *Ribeiroia ondatrae*

% studies   0   25   50   75   100

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 at the top of each panel, and the scale of dependent variables is indicated at 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, and shaded areas indicate that there was at least one. The intensity of shading indicates the proportion of studies in a certain system that fell into the corresponding category. A color version of this figure is available online.

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 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 a context that reflects natural transmission, for measures of parasite fitness such as parasite growth rate and virulence change greatly in a nonnatural context (Fenner 1947*b*; Spence et al. 2013).

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 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 *Hymenolepis diminuta* (Keymer and Anderson 1979), *Gyrodactylus* sp. (Scott and Anderson 1984), and *Heligmosomoides polygyrus* (Keymer 1985) systems. Indeed, in 1985 Keymer wrote a manifesto of sorts, outlining why epidemiological study systems were required and what they should look like (Keymer 1985)—arguments that stand the test of time and resonate with the arguments made herein. She argued that experimental epidemiological systems must allow the collection of data on "the complete epidemiological behavior of the parasite in its host population" (i.e., epidemic level data), and "the experimental study of population parameters . . . their dependence on, and interactions with other biological processes and . . . physical variables" (p. 56; i.e., individual, ex-host-level data). That is to say, with such a system one can isolate the effect of factors predicted to influence epidemic dynamics (e.g., host genetic variability), tease apart how combinations of factors manifest as epidemiological dynamics, and model variation that does not (yet) appear in nature. Indeed, experimental epidemiological studies could represent an additional complementary source of high-quality data that could be used to widen the canon of theoretical epidemiology, which is dominated by diseases that are viral and acute

and that often target juveniles (Keeling and Rohani 2011). As such, experimental epidemiology can not only help to reveal the mechanisms underlying the dynamics we observe in nature but illuminate what could be possible in nature, in all its diversity.

Filling the Transmission Gap Could Boost Vertical Integration in EEID

A further advantage of boosting the capacity to study epidemics in the laboratory is that it will permit the mechanistic investigation of feedbacks between small-scale within-host processes and larger-scale epidemiological processes; that is, it will fill the bottom left of the heat maps in figure 3. The study of interchange between processes at these scales has been the subject of much recent theoretical investigation but is difficult to achieve in the field (Day et al. 2011; Mideo et al. 2013; Childs et al. 2019). Take the evolution of drug resistance as an example. Recent theoretical studies have suggested that depending on the prevalence of circulating strains, within-host competition might alter the selective benefit of using different drug-dosing regimens (Hansen and Day 2014). Manipulating dosing regimens and/or epidemiological parameters can be unethical and extremely difficult in human populations, where there are also considerable challenges distinguishing between de novo and acquired resistance. An experimental system in which one could track the population dynamics of parasites within host, as well of those of hosts and parasites at the epidemic scale, would be invaluable in testing and expanding this theory.

The development of systems in which we can study the interactions and feedback between processes at the within-host and population scale (and even at larger scales) may be inherently difficult, however, because the traits that make it good for one come at the disadvantage of the other. On the one hand, to facilitate the study of epidemic dynamics hosts must be small enough that replicate, dense populations can be established, housed long term, and manipulated. On the other hand, the study of within-host dynamics over time in individual hosts requires that hosts be robust enough to be repeatedly handled and sampled. Pathosystems of large insects of agricultural importance may fall into this crucial sweet spot. Indeed, early work with *Tribolium* contributed to the understanding of the dynamics of host and parasite populations (Park 1948; Keymer and Anderson 1979), and they have recently been established as an ecological-evolutionary-immunological model (Tate and Graham 2017; Jent et al. 2019). As Keymer (1985) pointed out years ago, vertebrate models of human disease are well placed for this work, since much is known about vertebrate immunity; the development of

tools to noninvasively track infection dynamics (e.g., quantitative polymerase chain reaction, in vivo imaging) and manipulate parasite and host genetics since then have only added to their advantages. Recent studies in which laboratory mice were "rewilded" in order to understand the relative contribution of environment and genetics to within-host interactions (Lin et al. 2020; Yeung et al. 2020) demonstrate the unique utility of laboratory mice for answering questions in disease ecology. Such studies might be extended to study the interchange between within-host and epidemic dynamics if technologies that permit cheap, regular, high-throughput sampling of individuals could be developed. These studies also demonstrate that leading model systems in the wider biological sciences might also be powerful systems for EEID research.

While it is clear that laboratory studies could be better harnessed to understand disease dynamics at or below the epidemic scale, it is not immediately obvious that they could illuminate epidemic processes at the scale "above" epidemics, especially the ecosystem level. Such experiments would necessitate the use of micro- or mesocosms (e.g., per Johnson et al. 2007). However, the suitability of these types of experiments for the study of ecosystem-level processes has drawn repeated criticism because often even very large mesocosms are incapable of capturing the spatial or temporal scale of the processes of interest, the diversity of organisms involved (particularly those at higher trophic levels), or physical and chemical structure of environments (Carpenter 1996; Schindler 1998). It may thus be best to reserve mesocosm-scale experiments for estimating parameters of mathematical models (e.g., the biomass of pathogens or the [change in] nutrient content of infected hosts) or to use them only where ecologically relevant effects are likely to be observed (e.g., in systems that involve pathogens of ecologically dominant hosts species and simple, linear food webs; Mitchell 2003; Duffy 2007; Borer et al. 2009).

Toward the Cryptic and Rare

Our review suggests that we are not using our model systems to their full potential for the study of interactions between parasites and host immunity and their contribution to eco-evo dynamics of disease. Of the studies we reviewed that addressed infections that do not resolve, few used measures of infection success that permit the investigation of host defenses other than those that make the host refractory to infection. For example, in studies of *Diplostomum spathaceum*, *Pasteuria ramosa*, and *Ribeiroia ondatrae*, parasite infectivity/host susceptibility was often measured as the proportion of hosts that bore parasites at the site from which the parasites leave the host. This measure confounds the process of parasite infectivity with the processes of development and migration and, on the other hand, suggests that there is no host defense other than that which prevents infection in the first place. However, host responses that destroy parasites after the parasites successfully penetrates the host are present in these systems (Hall and Ebert 2012; LaFonte and Johnson 2013). Methods for explicitly measuring a parasite's progress through the host—for example, imaging of fluorescent parasites (e.g., Duneau et al. 2011; LaFonte and Johnson 2013)—and mathematical models that can quantitate how the hosts resist and tolerate infection (e.g., Wale et al. 2019) could refine our understanding of which traits mediate parasite and host fitness at each stage of the infection (Duneau et al. 2011). Indeed, there is much to gain from the methodologies used in cellular and molecular biology, such as fluorescence-based microscopy and cytometry as well as that field's mechanistic understanding of host-pathogen interactions. By harnessing these methods and insights, we can increase our ability to observe, quantify, and manipulate the phenotypes of interest to EEID as well as promote the vertical integration of infection biology as a whole.

There is work to do in systems where hosts can recover from infections too, specifically in the area of chronic infections. Among those infections where hosts can recover, low-level chronic infections of multiple weeks to years can develop in at least some animals (Hawley et al. 2005; Achtman et al. 2007; Sakala et al. 2015). Yet we recovered few studies in which these chronic infection dynamics were the subject of study, despite the fact that chronic infections can make substantial contributions to the maintenance of disease in an epidemic context and alter the measured shape of virulence-transmission relationships. No doubt, chronic infection studies are rare because, by definition, they take time. We must be careful not to take shortcuts, however; as our cousins the immunologists have learned, attempts to accelerate the development of chronic infections by using a larger pathogen inoculum than normal leads to qualitatively different immune responses and so defeats the whole exercise (Vidlak and Kielian 2016).

While studying only the immunological phenomena that are easy to observe could skew our understanding of EEID, omitting rare events is also an important gap. In his *Evolutionary Biology of Parasites*, Price (1980, p. 175) noted, "The ecology of rare events, an important aspect of life for parasites, is yet to be developed." One such rare event of importance in EEID is host range shifts, whose rarity as a subject of study among the studies we reviewed is notable given their importance to public and animal health. Host shift events are the subject of intense study, much of which focuses on host shifts that have happened and the development of methods to predict when and where they will occur next (e.g., Becker et al. 2019 and references therein). However, the relative rarity with

which host shifts occur makes them difficult to observe (at least in an unbiased way) in nature. As such, host shifts must be the object of experimental model systems research. Such research can complement retrospective research on host shifts by providing quantitative information about the probability of unobserved events, such as the failure of a pathogen to spill over, as well as mechanistic explanations for spillover (and its absence; Parrish et al. 2008; Gostic et al. 2019; Mollentze et al. 2020). Some models will be better than others for studying rare events like host shifts and other rare events, such as the addition or loss of host species as hosts or of transmission modes. We should prioritize systems where particularly vast sample sizes can be generated (e.g., *Drosophila* viruses; Longdon et al. 2011, 2015) and where the pathogen can be safely contained (see discussions related to gain-of-function experiments; Duprex et al. 2015).

Toward Horizontal Integration or the Comparative Study of EEID

While our review was not designed to uncover comparative research, it is clear from reading the studies that we often do not perform research with a comparative mindset or with reference to an infrastructure that would facilitate such an approach to research.

Yet comparative studies could help us draw general lessons about EEID, as a number of recent studies have demonstrated (Leggett et al. 2012; Acevedo et al. 2019), and our review shows that there is ample room to use experimental data in this manner, at least regarding questions of (the interactions between) individual-level disease processes (fig. 3). 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. For example, 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, we need (i) standardized experimental protocols and (ii) the infrastructure for sharing and storing protocols, the data generated, and the resources produced, such as parasite and host strains.

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 be used to better understand the nature of host-parasite interactions within the host (Moore et al. 2020; P. A. Clay, M. H. Cortex, and M. A. Duffy, unpublished manuscript). In a "standardized" dose-response experiment, 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—for example, might we consider varying the dose with reference to host biomass or metabolic rate, in the interests of understanding the energetic requirements of maintaining an infection? Theoretical models could help answer such questions of experimental design—for example, in this case by identifying maximally informative dose ranges in different host-parasite systems—as well as aid in the proper interpretation of the data they produce. In addition, theory plays a key role in providing precise definitions of key terms, without which we cannot hope to make comparisons between studies. Our review suggests that common definitions are greatly needed since there was great variation in the way even the most commonly invoked and important concepts in EEID were defined. For example, in the articles we reviewed, virulence was defined in the same way that we have used it here as well as to mean the harm an infection causes to the host (without respect to what caused it), the capacity for a parasite to infect a host (Flor 1958; Barrett et al. 2007), and the capacity for a parasite to kill a host (Fenner 1949*c*).

In addition to standardized experimental designs, an infrastructure for the collation, storage, and sharing of protocols, data, and resources could substantially advance comparative studies in EEID. The sharing of protocols and data is now easily facilitated by open source repositories such as protocols.io and datadryad.org. Yet the collation of such data into a cohesive data set is still an enormous challenge, albeit one with significant payoffs, as the Global Mammal Parasite Database demonstrates (Stephens et al. 2017). Other collaborative efforts, such as NutNet, serve as instructive examples of how to systematize the entire process of research, from the design of experiments to data sharing, as well as the advantage of doing so (Adler et al. 2011; Fraser et al. 2013). In addition to sharing of experimental designs and data, sharing of organisms will also facilitate the expansion and replication of EEID research. Across the biological sciences, strain banks enable scientists to readily obtain specific strains of an organism, and indeed, *Plasmodium chabaudi* and *H. polygyrus* can be thus acquired. However, the studies reviewed herein often use pathogen/host strains that are neither standardized (e.g., experimental infections are often generated using isolates, which can contain multiple pathogen genotypes; Luijckx et al. 2010) nor broadly sharable. The use of

polyclonal inocula or a diversity of hosts is often entirely appropriate for the questions at hand. But where possible, the collection, preservation, and maintenance of excess source organisms would enable post hoc isolation of genetically identical strains for comparative work. Establishing infrastructure for the sharing of data and resources will help us to replicate experiments, widen and democratize access to research resources, and, most relevant to the theme of this article, generate general insights about disease processes.

Part III: Developing Criteria for Model Systems in EEID

In parts I and II, we used a concept of model systems borrowed from the biomolecular sciences as a reference point for a discussion about what ecologists and evolutionary biologists of infectious disease use model systems for and how they might use them better. But EEID has a different outlook and different priorities than the cellular, molecular, and developmental fields of biology. Right off the bat, it was clear that this biomolecular conception of model systems was not a perfect fit. Model organisms in genetics, for example, are "not primarily studied because they are interesting in their own right" (Ankeny and Leonelli 2011, p. 318). By contrast, many of the model systems in EEID were established and are studied precisely because they are fascinating examples of evolution's mischief or because they are of medical, agricultural, or conservation concern. As such, experimental systems in EEID both serve as interesting foci and are used to elucidate general rules about infectious diseases. This illustrates that EEID as a field may want to establish a bespoke definition of what a model system is and what it can be used for. In this part of the article, we highlight issues that other fields have had to confront in their discussions about model systems as a jumping off point for our own.

The essential idea that underpins model systems research is that we can learn about the general principles of nature from organisms that have features that make them well suited to research because these model organisms share key features with other, less easily studied organisms (Krebs 1975). That is to say, model organisms are representative of other organisms. Holmes (1993) traces this idea to Aristotle's observation that different organisms share consistent body plans, and of course we now know that such similar traits are often (though not 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—for example, can one virus be a useful model of viruses only 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 modified to explain the dynamics of a variety of pathogens, including, for example, 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 and May (1991) suggests that systems might be usefully grouped for comparative purposes into the categories of microparasite versus macroparasite. Indeed, in performing this review, it felt unnatural to lump together the replication of microparasites and the 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— for example, complex versus simple and obligate versus nonobligate killer—which can greatly impact ecological and evolutionary dynamics (e.g., O'Keefe and Antonovics 2002). Importantly, it may not be enough to consider the traits of just parasites. EEID, unlike anatomy, genetics, and 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—for example, a measure of the relative speed of pathogen and host evolutionary rates—to elucidate which systems are representative of one another.

Much of the recent debate about the representativeness of model systems has focused on the extent to which the traits that make models easy to study also make them unrepresentative of organisms at large and so bias the picture they give us of the natural world (Alfred and Baldwin 2015). For example, in his classic article on what makes a model system, Krebs (1975) noted that one thing that makes model systems useful is the "magnitude of the phenomenon to be studied"—that is, that the model systems possess the trait of interest in abundance. Recently it has been argued that organisms possessing extreme characters may be very derived, originating in relatively unusual unconstrained ecological and evolutionary contexts, and so are ill representative of (the processes that generate) biodiversity at large (Alfred and Baldwin 2015). This idea has driven a push toward extending the taxonomic sampling in genetics and other fields.

The extent to which the model systems reviewed here are biased deserves debate, as will the biases generated by

any future-defined selection criteria for model systems. Ironically, the lack of a well-defined notion of a model system may have spared EEID some of the problems that arise as a result of the biased sampling of systems in other fields, whereby they exhibit only the very extremes in the traits of interest or a specific taxonomic group. The majority of systems reviewed here were first studied in another disease-focused field, such as parasitology or immunology; as models of a specific disease; and/or because of their applied importance (table 1). Thus, while they are united in being pathogenic, they represent a relatively random taxonomic set and, unlike many infections studied in the biomedical sciences, do not represent the most pathogenic of diseases. This set of pathosystems may not represent infectious diseases in other ways, however, most obviously because traits that make them easy to study in the laboratory may not be widely distributed in nature. For example, as we have noted, in many of the systems reviewed the (most commonly studied) host cannot fully recover. This feature makes these pathosystems easy to study—they can be modeled using a simple SI framework and, in the context of laboratory studies of epidemics, reduce the time required for sampling, since researchers need to track individuals only until infection is confirmed.

Are these systems thus unrepresentative of the many infections that do resolve? In some ways, certainly. But that does not mean that they entirely uninformative about the process of recovery. Take an analogy from evolutionary developmental biology. Jenner and Wills (2007) countered the argument that systems invulnerable to environmental change were poorly placed for understanding environmental influence on development by noting that such systems could help evolutionary developmental biologists understand the complementary phenomenon of canalization. In a similar vein, nonresolving diseases might help illuminate much about tolerance, a host response that is complementary to, and coexists alongside, resistance.

Indeed, it might be argued that the ways in which model systems fail to represent other systems are just as useful, if not more useful, than the ways in which they are. Take the example of *Melampsora lini* and *Pasteuria ramosa*. Interactions of these two pathogens and their hosts are mediated by "matching" interactions between their genes and those of their hosts. These systems are often used by EEID researchers to ask similar questions, for example, about the impact of space and metapopulations on disease dynamics. Yet their coevolutionary dynamics are different because of the details about what happens when a parasite and host genes match (mediating incompatibility and compatibility, respectively; Thrall et al. 2016). Thus, details matter, and they teach us where our theory falls down and motivate us to make it anew.

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 laboratory, 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 we want from our model systems could help to establish concrete, consensus definitions of concepts or experimental designs that could be used across model systems in EEID.

Statement of Authorship

N.W. conceived of the framing of the article, performed the literature review, and wrote the manuscript. M.A.D. provided feedback on the framing of the article and edited the manuscript.

Data and Code Availability

A list of the references reviewed as part of this article are available in the Dryad Digital Repository (https://doi.org/10.5061/dryad.fbg79cntb; Wale 2021).

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