Received: 20 April 2020 | Accepted: 14 April 2022

DOI: 10.1111/1365-2435.14065

Functional Ecology | BRITISH ECOLOGICAL SOCIETY

REVIEW

# Exposure and susceptibility: The Twin Pillars of infection

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**Funding information**
NERC, Grant/Award Number: NE/R016801/1; College for Life Sciences Fellowship

**Handling Editor:** Dana Hawley

## Abstract

1. Exposure and susceptibility underlie every organism's infection status, and an untold diversity of factors can drive variation in both. Often, both exposure and susceptibility change in response to a given factor, and they can interact, such that their relative contributions to observed disease dynamics are obscured. These independent and interlinked changes often complicate empirical inference in disease ecology and ecoimmunology.
2. Although many disease ecology studies address this problem, it is often implicit rather than explicit and requires a specific set of tools to tackle. Moreover, as yet, there is no established conceptual framework for disentangling susceptibility and exposure processes.
3. Here, we consolidate previous theory and empirical understanding regarding the entwined effects of susceptibility and exposure, which we refer to as 'the Twin Pillar Problem'. We provide a framework for conceptualising exposure–susceptibility interactions, where they obscure, confound, induce or counteract one another, providing some well-known examples for each complicating mechanism.
4. We synthesise guidelines for anticipating and controlling for covariance between exposure and susceptibility, and we detail statistical and operational methodology that researchers have employed to deal with them. Finally, we discuss novel emerging frontiers in their study in ecology, and their potential for further integration in the fields of wildlife and human health.

**KEYWORDS**
disease control, disease ecology, ecological immunology, ecological statistics, exposure, host–parasite interactions, susceptibility, wildlife disease

## 1 | THE TWIN PILLAR PROBLEM

An animal's disease burden is defined by two fundamental host-mediated components: its exposure to infective parasites, and its susceptibility to infection after exposure (Downs et al., 2019; Hawley & Altizer, 2011; Sheldon & Verhulst, 1996; Stewart Merrill et al., 2019, 2021). Simply examining heterogeneity in parasitism across a population is insufficient to identify the mechanisms producing it, because

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variation in both intrinsic susceptibility and extrinsic exposure could drive the observed patterns. We refer to this long-recognised problem as the 'Twin Pillar Problem' because without either susceptibility or exposure, infection cannot occur, but it is difficult to identify observationally which pillar bears more weight. An ever-present problem for disease ecologists running individual-based analyses, the Twin Pillar Problem has a series of implications for most questions in the field: most notably, failing to consider or measure both can result in inference of susceptibility effects where in fact exposure is responsible, or vice versa. As such, understanding and considering both processes is fundamental to epidemiology and disease ecology, and can drastically affect the accuracy of epidemiological models. Decomposing susceptibility and exposure can lead to important conclusions concerning disease transmission (Buck et al., 2017; Civitello & Rohr, 2014; Stewart Merrill et al., 2021). For example, Stewart Merrill et al. (2021) measured both exposure and susceptibility components across *Daphnia* populations alongside epidemiological parameters to train epidemiological models. These models were used to draw broad conclusions about how host and environmental factors drive epidemic dynamics, revealing that asynchronicity in exposure and susceptibility can inhibit outbreaks. Important interrelationships like these are likely the rule rather than the exception; however, as yet, there has been no full consolidation of the challenges involved when disentangling exposure and susceptibility, and the wide range of approaches used to address them.

Both susceptibility and exposure respond to myriad ecological factors, and can do so independently or synergistically (Hawley & Altizer, 2011; Sheldon & Verhulst, 1996). Consequently, their signals interfere with each other, complicating mechanistic inference. Often researchers are interested in quantifying variation in susceptibility in the wild, yet uncontrolled variation in exposure gets in the way, reducing certainty about the magnitude of detected susceptibility effects (Ezenwa, 2004; Ferrari et al., 2004). In contrast, some systems emphasise exposure's importance: most notably, many human public health interventions are designed to prevent pathogen exposure (e.g. using bed nets to exclude malaria vectors; Killeen et al., 2007), rather than focussing on bolstering immunity to said pathogens. Nevertheless, integrative disease control strategies can benefit greatly from taking both Pillars into account: for example, responses to SARS-CoV-2 have revolved around a vital combination of non-pharmaceutical behavioural interventions (to reduce exposure) and vaccination regimes (to reduce susceptibility).

In public health, both exposure and susceptibility are important to consider, and the public hold an intrinsic understanding of their joint role in driving epidemics (Figure 1). However, their relative importance is often poorly understood, potentially fuelling inequity in health solutions. For example, individual susceptibility is commonly referenced in the context of 'boosting' one's immune system via supplements. Such an emphasis risks misrepresenting the magnitude of effect that such measures are likely to have on disease outcome, particularly compared to vaccine-mediated changes in susceptibility or effective exposure reduction (Figure 1). Similarly, lower income individuals are more susceptible to infection with influenza regardless of exposure (Cohen et al., 2008), which contributes heavily to socioeconomic disparities in influenza rates in the United States (Zipfel et al., 2021). Strikingly, ameliorating these susceptibility differences could reduce disease burden at least as much as exposure-based control (Zipfel et al., 2021). In the case of soil-transmitted helminths, the best and most geographically equitable interventions involve both exposure reduction via water and hygiene initiatives (breaking the transmission cycle; Koski & Scott, 2001) and immune supplementation through increased nutritional availability, with potentially synergistic results (Sweeny, Clerc, et al., 2021). These and other examples demonstrate that an accurate understanding of susceptibility, exposure and their interactions can be vital for implementing effective disease control interventions and reducing inequality.

Designing integrative interventions first requires that researchers untangle exposure and susceptibility processes in their focal system, necessitating a fundamental understanding of the theory behind the Twin Pillar Problem. Studies regularly acknowledge both processes explicitly—and even more so implicitly—and models offer means of dealing with both. Like many fields, disease ecology supports a complex lexicon of terminology that can result in confusion when terms are used inconsistently or interchangeably. As such, to discuss the Twin Pillar Framework, we must agree on


**FIGURE 1** The Twin Pillars on the street. Messaging in public health often revolves around public responsibility in reducing exposure (left) while private companies may advocate for personal benefits of reducing susceptibility (right). Understanding the reality of both components can be invaluable for understanding disease dynamics, and for reducing inequity in health solutions. Both photos were taken in the United States in late march 2020, during the SARS-CoV-2 pandemic. Photo credit: Jeanmarie Evelly (left); Greg Albery (right)

a series of definitions. First, we define '**exposure**' as a host's encounter rate with an infectious pathogen. In this way, an '**exposure event**' represents a host's encounter with an environmental pathogen or infected conspecific that could allow the pathogen to invade and establish an infection. The extent of successful infection given exposure, often quantified via pathogen intensity or load within a host, depends on a variety of barriers and within-host traits that we define loosely as '**susceptibility**'. This definition is widely used, and can be considered the inverse of '**resistance**' (Graham et al., 2011). To frame them another way, the terms '**exposure**' and '**susceptibility**' as we use them broadly represent '**between-host processes**' and '**host-level processes**' respectively. Similar suitable conceptualisations are **extrinsic** versus **intrinsic** host processes, or **opportunity** versus **compatibility** filters (Combes, 2001). Importantly, variation in these processes does not necessarily occur at the same level as their drivers: for example, exposure can be governed by personality (predominantly an intrinsic trait), while susceptibility can depend on the distribution of resources (an extrinsic factor) as well as intrinsic drivers. Furthermore, there are a range of other finer-scale epidemiological processes and parameters of interest—which we do not focus on, but which may be of interest in future studies (see Section 4C). For example, within-individual pathogen proliferation (i.e. 'suitability') and limitation of parasite-induced harm with increasing infection intensity ('tolerance') may further shape relationships among exposure, susceptibility and infection. Although the interactions between within-host dynamics and between-host processes are often confounded, their interplay is well-recognised as an important component for overall transmission and epidemiology (Handel & Rohani, 2015).

## 2 | CASE STUDIES OF EXPOSURE–SUSCEPTIBILITY RELATIONSHIPS

Susceptibility and exposure are interrelated in many natural systems, such that they can interact or change separately, and in the same or opposing directions. A foundational aspect of this relationship is that in the absence of exposure, variation in susceptibility across or within individuals would be unobservable, and therefore studies of susceptibility must rely on some level of exposure (Figure 2). Beyond this initial revealing, however, the relationship between the two can involve multiple mechanisms characterised by the causal relationships between stimulus, exposure and susceptibility (Figure 3). Here, we focus primarily on wild, observational systems in which it is difficult to experimentally control for either component. In this section, we describe generalised example relationships between the two that can create confusing or opaque patterns in wild animals (in italics below). We further elaborate on each concept with illustrative examples in wild animals (in bold below), to demonstrate how these difficulties can manifest in real-life scenarios. Finally, having described the four mechanisms, we outline two specific example scenarios (ageing and seasonality effects) in which multiple potential explanations are possible.

### 2A. Exposure induces variation in susceptibility

***Exposure induces components of the immune response, revealing variation in susceptibility across or within individuals that would otherwise be unobservable. Extraneous variation in exposure rate can therefore drive an observed relationship between a stimulus and susceptibility (Figure 3a).***

Because exposure rate can determine observable variation in susceptibility, experimental studies commonly involve actively manipulating exposure rates to reveal variation in susceptibility. This approach relies upon exposed individuals expressing immune responses, which are then quantified alongside infection metrics to obtain an idea of susceptibility. In natural animal populations, measures such as antibody levels often connote past exposures (i.e. seropositivity). Although an exposure event is necessary to reveal variation in susceptibility, inference of meaningful variation in the wild can be obscured by noise from variable infection dates and dose, the implications of which have been well-discussed elsewhere (Figure 3a; e.g. Gilbert et al., 2013).

Most pressingly, because the immune system evolved partly to combat infection, many elements of immunity are upregulated in response to parasite exposure. Where a study aims to identify immune correlates of parasite burden (i.e. susceptibility), this mechanism can cause problems because more-exposed individuals may in fact display greater immune expression (because exposure induces immune expression) *and* greater parasite burden (because their greater exposure rate leads to greater burden). This creates an apparent positive correlation between immune expression and parasites, which might obscure any real effect of susceptibility on infection (Figure 2). For example, Ezenwa (2004) found that helminth faecal egg counts in wild bovids were higher under drought conditions and in individuals with lower dietary protein. They attributed this difference largely to reduced protein intake during dry periods and variation in susceptibility due to nutrition quality; however, although the authors considered it unlikely, it was also possible that drought conditions caused hosts to be exposed to greater numbers of infectious larvae (Ezenwa, 2004).

### 2B. Exposure and susceptibility are positively correlated

***Both exposure and susceptibility potentially change in the same direction according to a priori mechanistic understanding, but it is unclear which of the two is acting in the focal scenario (Figure 3b).***

**Reproductive trade-offs** provide an example where susceptibility and exposure confound each other by changing in the same direction (Figure 3b). Reproductive individuals generally exhibit increased parasite burden, which is commonly attributed to weaker resistance as a result of resource reallocation away from the immune system (Knowles et al., 2009; Sheldon & Verhulst, 1996). However, in addition to increased risk of directly and sexually transmitted infections, reproductive individuals may also need

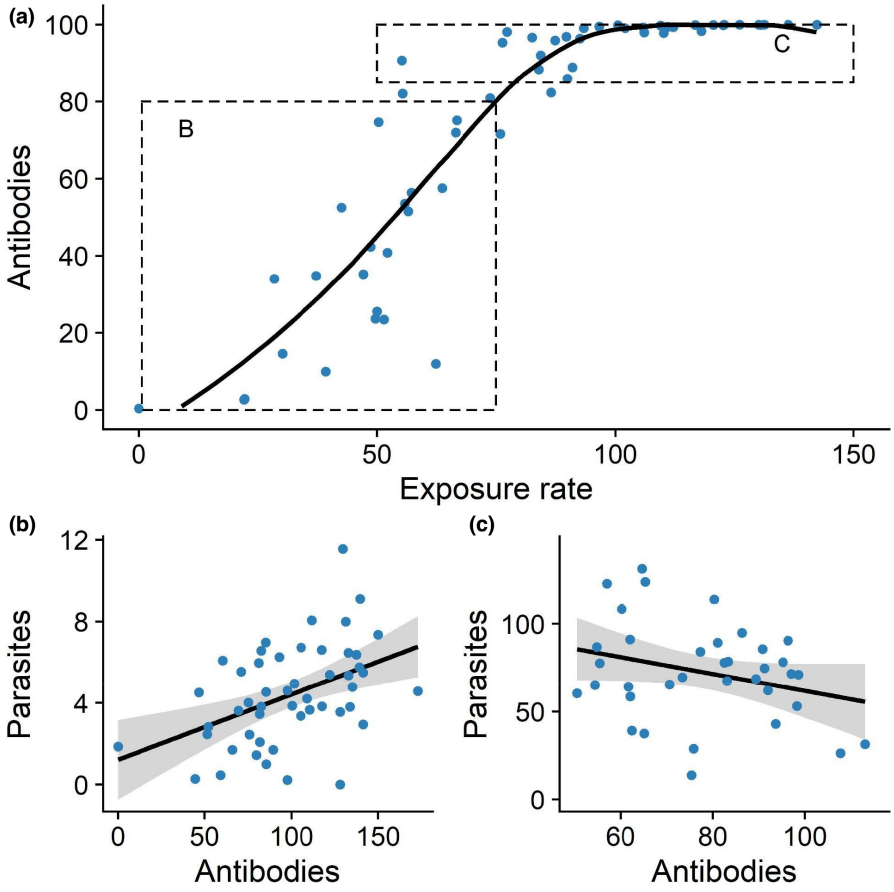


**FIGURE 2** Observed immunity–parasitism relationships depend on the subset of the data selected, because exposure rate affects the expression of inducible immune components. These panels display simulated data representing hypothetical simplified relationships between exposure and susceptibility at different exposure rates, using antibody responses and parasites (both in arbitrary units) as an example. Panel (a) represents the relationship between parasite exposure rate and immune expression across the population, where greater parasite exposure rate induces greater antibody levels. Each point represents a measure from a different individual. The boxes in panel (a) represent the subset of the population displayed in panels (b) and (c). In panel (b), exposure rate is relatively low, and researchers will observe a positive correlation between antibodies and parasites because greater exposure rate has driven greater immune expression across the population. In contrast, panel (c) represents a scenario where all individuals have been exposed to a similar level and those that express greater antibody levels exhibit lower burdens because they have lower susceptibility

to move and forage differently (Speakman, 2008), and spend more time in close proximity to young animals, which are often heavily infected (Ashby & Bruns, 2018). Therefore, increased exposure associated with reproduction is an equally plausible candidate (Albery, Watt, et al., 2020; Knowles et al., 2009; Sheldon & Verhulst, 1996). Consequently, reproduction-associated increases in susceptibility and exposure may be completely confounded, and researchers can only make confident inference by measuring both (e.g. by quantifying immune expression or movement as well as parasitism; see below). For example, testosterone is generally expected to have immunosuppressive effects on hosts, increasing susceptibility (Folstad & Karter, 1992). However, testosterone-treated male wood mice increased their social contacts and by extension transmission potential, highlighting possible confounding between susceptibility and exposure effects (Grear et al., 2009). Similarly, in wild red deer, reproduction-associated increases in helminth egg count were not solely explicable through reproduction-associated reductions in antibody levels, implying an important role of exposure through altered grazing behaviours (Albery, Watt, et al., 2020). Although we use reproductive trade-offs as an example here, this point may generalise to many other physiological and behavioural trade-offs: for example, individuals with more extroverted personalities may be more active, expending more energy and increasing their susceptibility (van Dijk & Matson, 2016), or they may encounter parasites more regularly by ranging further and making more contacts (Barber & Dingemanse, 2010).

## 2C. Exposure and susceptibility are negatively correlated

***Changes in exposure and susceptibility have opposing effects on parasite burden, but one effect is larger than the other, so only one is observed. Alternatively, no effect may be observed (or deemed significant) where in fact both susceptibility and exposure are being altered (Figure 3c).***

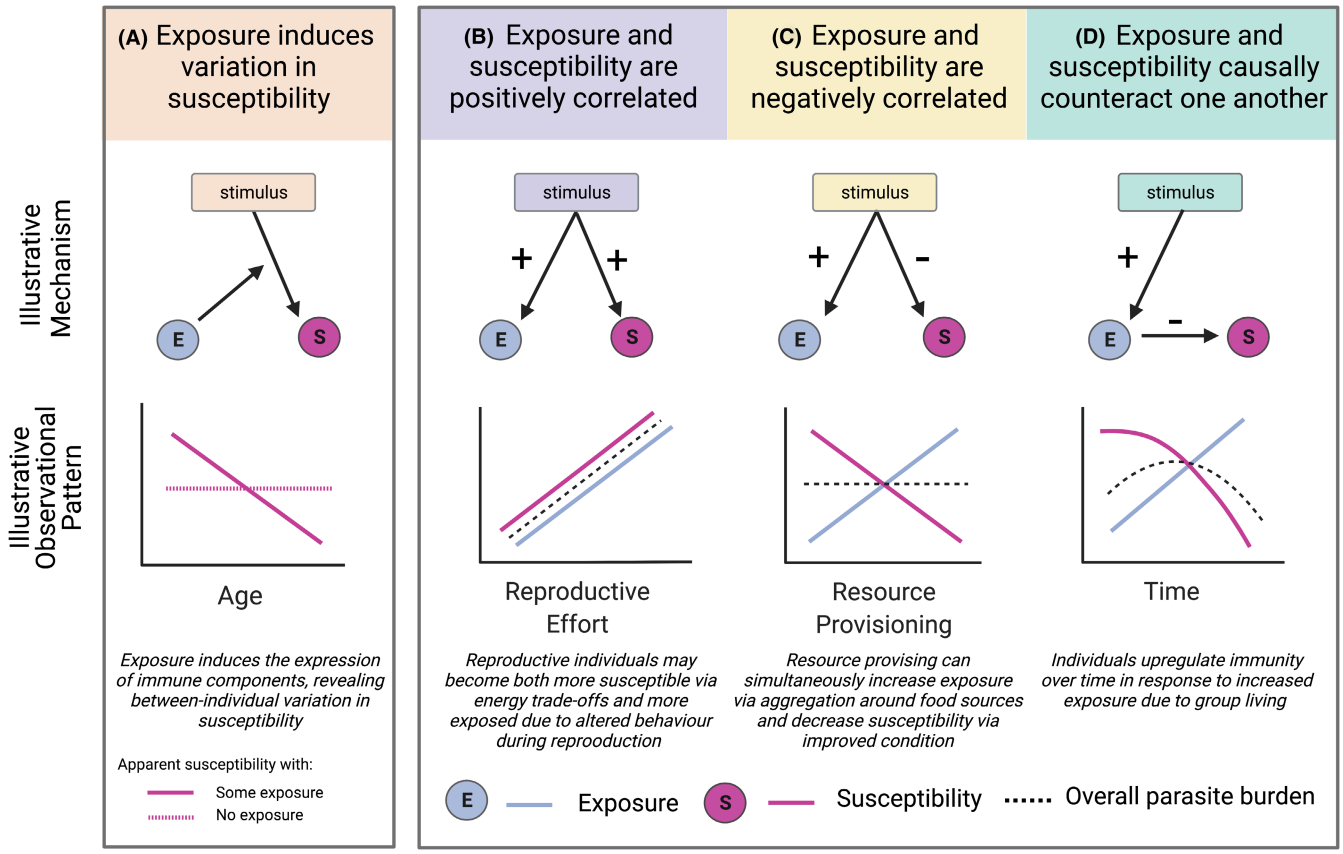


FIGURE 3 Illustrative examples of covarying exposure (E) and susceptibility (S) trends driven by a range of factors, and their relationships with overall parasite burden. Top row: Simplified pathways describing the mechanism of each process. Bottom row: Each stimulus is on the x axis, and its effects on parasitism according to exposure- and susceptibility-driven scenarios are represented by the different coloured lines (blue = exposure-driven; pink = susceptibility-driven). NB these are not exhaustive: For example, in B the stimulus's effects on susceptibility and exposure can both be negative, and in D changes in susceptibility can counteract exposure. Further explanation is in Section 2 in the main text

**Resource supplementation** can have obscuring effects, potentially acting on susceptibility and exposure in alternate directions (Figure 3c). On one hand, increased resource availability is expected to have positive effects on host physiology and therefore on immune resistance, reducing parasite burden (Strandin et al., 2018). On the other hand, the quantity and quality of resources can have dramatic consequences for host behaviour, reproduction, and survival, increasing density and aggregation around introduced food sources, and thereby increasing exposure to parasites in the environment or from infected conspecifics (Becker et al., 2015, 2018). The balance of these processes will determine the outcome of resource supplementation for parasitism: in wild wood mice, supplementation substantially reduces helminth burden via increased condition and anti-helminth immunity despite higher population densities on supplemented grids (Sweeny, Clerc, et al., 2021). In contrast, resource supplementation in house finches *Haemorhous mexicanus* increased transmission of the bacterial pathogen *Mycoplasma gallisepticum*, likely due to aggregation at feeders (Moyers et al., 2018). A longitudinal study of 11 wild bird species further described these obscuring forces, where infectious disease prevalence increased in birds supplemented by feeders despite increased health and condition (Wilcoxen et al., 2015). Host resources can influence pathogens directly, where within-host energy influences energy available for the pathogen to divert for replication; increased resource availability can therefore increase host parasite burden despite condition benefits (decreased susceptibility) for the host (Cressler et al., 2014). The outcome of resource supplementation for wildlife disease therefore depends on a combination of factors affecting both susceptibility and exposure processes, but empirical studies are often unable to examine and weigh the contributions of their potentially opposing effects (Becker et al., 2015; Becker & Hall, 2014).

## 2D. Exposure and susceptibility actively counteract one another

***Increased susceptibility or exposure invokes a feedback response, which then affects one or both of them, eventually influencing infection in the opposing direction. This is the most complicated of the mechanisms, and generally requires a timeline to understand. This mechanism is distinct from 2B in that 2D is causal (changes in susceptibility or exposure***

***invoke changes in the other) rather than correlational (susceptibility and exposure change concurrently but independently) (Figure 3d).***

**Density-dependent prophylaxis** presents a scenario where exposure and susceptibility effects actively counteract each other in a time-structured and potentially adaptive manner (Figure 3d). Although increased population density often exacerbates exposure by increasing rates of between-individual encounters (Cote & Poulin, 1995), individuals may respond pre-emptively to increased density by upregulating their immune resistance expression, thereby decreasing their susceptibility (Elliot & Hart, 2010; Wilson & Cotter, 2009). For example, desert locusts *Schistocerca gregaria* reared under greater densities became more resistant to the fungal pathogen *Metarhizium anisopliae*, as a result of upregulated immune defence (Wilson et al., 2002). In canaries, the mere sight of a sick conspecific promotes the upregulation of immunity (Love et al., 2021). In situations like these, researchers may observe negative correlations between density and pathogen prevalence—that is, where density produces increased immune expression, decreased susceptibility and reduced parasite burden—despite the fact that this increased density is increasing exposure.

The converse can also happen, where an animal seeks to counteract an increase in susceptibility by decreasing exposure, through either disgust or sickness behaviours (Curtis et al., 2011; Hart, 1988; Lopes, 2014). For example, in humans, anorexia and vomiting in pregnancy may represent a preventative measure to avoid exposure to pathogens during immunosuppressed periods (Fessler et al., 2005). Similarly, exposing animals to immune agonists or infections often results in reduced sociality and anorexia (Hart, 1988; Lopes, 2014), which may serve to reduce exposure to novel parasites and avoid compounding the problem.

In general, counteracting mechanisms are similar to mechanism 2A in that they represent time-structured, causal interactions between exposure and susceptibility, but in this case the process occurs adaptively and without direct exposure-related mediation. That is, exposure itself is not necessarily inducing a change in susceptibility, only the threat of greater exposure posed by a given stimulus (e.g. the presence of conspecifics, reduced immunity in pregnancy or the presence of a coinfecting pathogen).

## Example challenges in characterising exposure–susceptibility relationships

### Age-related changes can produce diverse patterns of exposure and susceptibility

For many biological phenomena, researchers may expect to encounter more than one of these covariance mechanisms. For example, host exposure and susceptibility commonly covary with host age, but in conflicting patterns (Figure 4a,b), covering the range of our outlined mechanisms (Section 2). Extremely young animals may not have yet been exposed enough to developed patent infections, and may therefore be uninfected—despite being highly susceptible due to their naive immune systems (Albery et al., 2018)—but this high susceptibility would be difficult to identify because of between-individual variation in exposure (Mechanism 2A). Conversely, older individuals may exhibit lower parasite burdens because they have acquired immunity throughout their lifetime, conferring decreased susceptibility, but the observed pattern will depend on the changing balance of exposure and acquired immunity (Mechanism 2C) (Woolhouse, 1992).

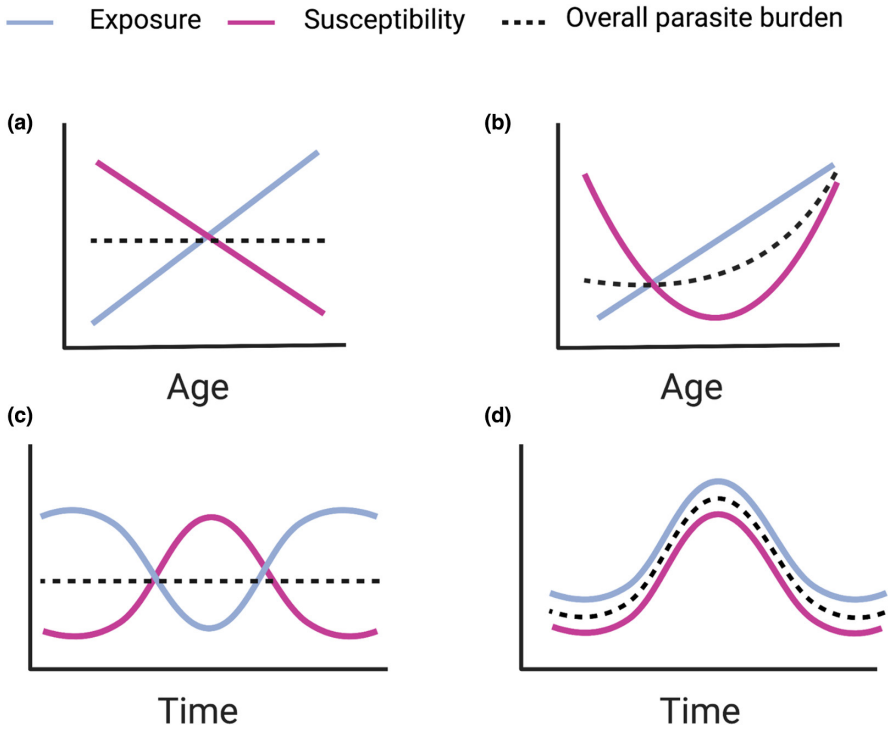


FIGURE 4 Illustrative examples of dynamic and context-dependent exposure–susceptibility relationships across the life span or through time (a, b). Panel (a) shows negative correlations between the two in both early and late life due to gradually decreasing susceptibility and increasing exposure. Panel (b) shows an initially negative correlation due to naïve immunity and low exposure progressing to a positive correlation over time as susceptibility increases again late in life along with exposure. NB: Exposure depicted as varying by age does not represent a cumulative metric. (c, d) Temporal (e.g. seasonal) fluctuations in parasite burden may represent either negatively (panel c) or positively correlated (panel d) exposure and susceptibility, dependent on host, parasite and environmental characteristics

The relationship between exposure and susceptibility can also change in nature over time. For example, exposure may induce immunity in early life (Mechanism 2A) and then susceptibility and exposure might obscure one another later in life (Mechanism 2C) when older individuals exhibit greater burdens due to immunosenescence (greater susceptibility; Figure 4a). Alternately exposure may continue inducing susceptibility but older individuals may gradually accumulate parasites, producing a positive correlation between susceptibility and exposure over the life span (Mechanism 2B; Figure 4b; Froy et al., 2019; Hawlena et al., 2006; Krasnov et al., 2005; Lutermann et al., 2012). For example, in small mammals helminth infection burdens increase with age due to increased foraging and exposure (Behnke et al., 1999). In longer-lived mammals such as Soay sheep, helminth burdens eventually increase with age due to immunosenescence-related greater susceptibility (Froy et al., 2019), but the extent of this increase further depends on the cumulative environmental stressors over an individual's lifetime (Hayward et al., 2009). As such, there may be extreme nonlinearity in the pattern of infection through an animal's lifetime depending on shifts in the balance of exposure- and susceptibility-mediated processes.

### Seasonality of exposure and susceptibility

Seasonal fluctuations of parasitism are near-universal (Altizer et al., 2006; Martin et al., 2008), offering an example of exposure and susceptibility being either positively or negatively correlated (Mechanism 2B,C; Figure 4c,d). An easy explanation for seasonality is that fluctuating abiotic factors alter transmission patterns, hindering parasite exposure at certain times of year and facilitating it at others (Altizer et al., 2006). However, immune systems also fluctuate seasonally (Martin et al., 2008), and observed patterns of seasonality are likely to be emergent phenomena that depend on a combination of host immune resistance and parasite transmission. A given parasite could therefore exhibit seasonality because the host allocates more to immune defence at certain times, or because environmentally varying factors and emergent fluctuations in exposure generate divergent benefits of immune investment at certain times of year (Martin et al., 2008). This mechanism begs the question: does parasite seasonality represent an adaptation of the host, the parasite, both or neither? Studies that quantify both immune expression and parasite burden can untangle these processes (see Section 3). For example, if parasites peak in the same season(s) as do functional resistance responses (e.g. as with gastrointestinal helminths in red deer; Albery, Watt, et al., 2020), seasonal fluctuations might be a parasite's adaptation to transmission through its environment, with hosts' immunity responding in kind. In contrast, if parasitism peaks when immune expression is lowest, as with influenza infection (Lowen & Steel, 2014), then weaker immune responses allowing greater burden could explain the fluctuations. Combining immune and parasite measures with quantification of specific environmental drivers may strengthen inference in this scenario (see Section 3.2).

Age and season therefore represent common instances where multiple non-exclusive processes may dictate infection outcome. What tools do researchers employ in these and other scenarios where exposure and susceptibility are intertwined?

## 3 | UNTANGLING EXPOSURE AND SUSCEPTIBILITY EFFECTS

Although the case studies above highlight the potential for susceptibility and exposure interrelationships to be vexing, researchers have developed many approaches to account for these problems empirically and analytically. Here, we outline some methods that researchers employ to help delineate the two, including use of laboratory populations, measurement of diverse traits and sophisticated statistical techniques.

**1: Experimental work in a controlled environment** can confirm whether infection changes when exposure is controlled for, implicating susceptibility (or vice versa). This approach can be used to directly replicate an observation from a difficult-to-manipulate wild system. For example, a recent study in wood mice *Apodemus sylvaticus* used laboratory replication to demonstrate that resource supplementation in the wild decreases helminth burden by reducing susceptibility rather than exposure (Sweeny, Clerc, et al., 2021). Similarly, rewilding laboratory mice into semi-wild enclosures and standardising exposure via experimental infection allowed identification of rapid environmental effects on helminth susceptibility (Leung et al., 2018). Further experimental approaches are used to investigate how parasite burden depends on exposure dose, by standardising susceptibility and applying a variable number of infective parasites (Ben-Ami et al., 2010; Langwig et al., 2017). These approaches can be highly useful for disentangling the Twin Pillars, yet are often impractical for multiple reasons: first, the parasite must be laboratory culturable for experimental infection, which is often not feasible. Likewise, the host must be tractable, excluding many (large) wild animals. Furthermore, laboratory-dwelling and wild animals of the same species may differ in terms of microbiota or immune phenotypes in ways that can worryingly undermine results (Budischak et al., 2018; Leung et al., 2018). Even in systems where laboratory replication or controlled environments are possible, the increased effort and resources required may necessitate considerably reduced sample sizes, so that findings are non-replicable due to reduced statistical power rather than due to altered mechanisms. As such, this approach may not be feasible or representative in many systems, in which case researchers should take multiple measurements of susceptibility and exposure and apply specific analyses designed to extricate the two.

**2: Take multiple types of measurements** to determine which of susceptibility or exposure effects are most likely to be acting, ideally including parasite-specific immune measures (Bradley & Jackson, 2008). Put simply, researchers can measure parasitism alongside expression of protective immune responses; if immune expression and parasites correlate negatively, and both change in

response to the varying factor as expected, susceptibility is likely to be responsible for the change in parasitism. If not, researchers can infer an important role of exposure. For example, Knutie (2020) investigated the effects of resource supplementation on parasitic blowflies in Eastern bluebird nestlings *Sialia sialis*. Under a 2×2 experimental design of supplementation and parasite removal, supplemented nests had significantly higher antibody levels and therefore reduced susceptibility, which resulted in 75% fewer parasites in these nests (Knutie, 2020). Unfortunately, these approaches rely on having well-understood immune measures to hand, which is often not the case (see below). Although immunity is considered an important component of a host's generalised susceptibility, particularly in mammal systems, it is important to note that there may be other salient components of susceptibility such as physical barriers, which are quantifiable in some systems (e.g. *Daphnia*; Stewart Merrill et al., 2019).

Conversely, quantifying exposure alongside parasitism can serve as an alternative to immune metrics, where deviations from expected parasitism-exposure relationships imply a role of susceptibility. First, exposure could be manipulated in some highly tractable systems, for example, in semi-wild mouse populations (Budischak et al., 2018), or in laboratory populations (see Section 2A). Where exposure is not directly manipulable, it may be measurable using metrics such as the attack rate of infective spores (Stewart Merrill et al., 2021). In the vast majority of systems where manipulation and direct observation of exposure are impossible, just as susceptibility can be approximated by immune- and barrier-related measures, exposure can be assessed using an individual's movements in space or contact with infected conspecifics or parasites themselves (Albery et al., 2021). Different types of contact will be meaningful for different parasites, and the information contained in these data can be leveraged to make stronger inferences. For example, because transmission of many parasites depends on host density, the local density of conspecifics could be used as a generalisable exposure proxy (Wilson et al., 2002). For vector-borne parasites, an individual's spatial proximity to the vector's (suspected) microhabitat could be used (Wood et al., 2007). Where the parasite is environmentally latent, researchers could directly quantify local parasite abundances by, for example, dragging for ticks, counting larvae on pasture or trapping vectors. Where possible, direct contact measures can be highly informative compared to behavioural proxies. For example, Hoyt et al. (2018) used fluorescent powder to identify skin-to-skin contacts, which was highly successful for identifying exposure events of white-nose syndrome in North American bats. Alternatively, if the transmission mode of the parasite is well-understood, specific environmental drivers such as rainfall may likewise be taken to represent exposure probability (Shearer & Ezenwa, 2020). Importantly, social behaviour can also covary with susceptibility, so social metrics may not solely represent variation in contact processes (Hawley et al., 2011). In these scenarios, where behaviour and susceptibility are expected to covary, measuring both immune expression and behaviour can be highly revealing (Albery et al., 2021).

One major hurdle to immunity-measuring approaches is the scarcity of reliable methodologies. Ecoimmunology has long faced challenges in developing tools suited to wild animals, and researchers often lean on veterinary resources developed in related species (Boughton et al., 2011; Garnier & Graham, 2014). As such, researchers' ability to untangle exposure and susceptibility approaches in their system might be limited in their available measures. Similarly, although behavioural studies are increasingly being facilitated by GPS tags and other biologging approaches (Kays et al., 2015; Smith & Pinter-Wollman, 2021), such technologies are still expensive, and often only involve tagging a subset of the population, and for a limited period before batteries become exhausted (Gilbertson et al., 2021; Tomkiewicz et al., 2010). Furthermore, even if both immunological and behavioural approaches are reliable, researchers may struggle to pair the two to achieve the strongest inference. Many GPS-facilitated studies sample a few individuals in a population that are then followed at high resolution from afar; in contrast, immunological studies often benefit from taking direct samples (e.g. blood, faeces or hair) from many individuals, which requires close spatial proximity and is often cross-sectional rather than longitudinal. These very different scales and patterns of investigation can be difficult to pair in large sample sizes, so there are relatively few analyses that combine the two, although the results can be highly informative (Albery et al., 2021).

**3: Use analyses that explicitly deal with exposure and susceptibility separately.** The field of ecological statistics has matured considerably since the identification of the susceptibility/exposure dichotomy, and previous work has highlighted the value of complex models in extricating susceptibility and exposure effects. Where it is impossible to methodologically confirm the presence/absence or rate of exposure (e.g. estimating contact rates in rodents to study hantavirus infection; Pearson & Callaway, 2006), models can incorporate susceptibility and exposure as separate parameters or components. Mathematical models can be used to simulate exposure and susceptibility-driven processes separately, potentially capturing epidemiological dynamics more accurately (e.g. Becker & Hall, 2014; Civitello & Rohr, 2014; Stewart Merrill et al., 2021). Predictions under various parameterisations can therefore be compared to real-world epidemiological outcomes to verify whether the Twin Pillars play important roles in the focal system.

Additionally, spatial, movement and social network analyses can be employed to untangle exposure and susceptibility in situations where transmission mode is well-understood. For example, Albery et al. (2019) used spatial autocorrelation methods to model fine-scale spatial variation in gastrointestinal helminth infection in wild red deer. By comparing the spatial distributions of helminths with those of protective immune measures (mucosal antibodies), the authors revealed strong discordance between patterns of susceptibility and parasitism, concluding that variation in environmental exposure was likely responsible for much of the spatial variation in infection. Where environmental drivers are the subject of the analysis, sliding windows can be employed to identify which of the pillars is responsible. For example, Shearer and Ezenwa (2020) set strong a priori

hypotheses for divergent effects of rainfall on susceptibility and exposure on helminth infection in Grant's gazelle *Nanger granti*. They used 0-, 1- and 2-month windows of rainfall to investigate whether rainfall had delayed, negative effects on infection (demonstrating that nutrition reduced susceptibility) or short-term, positive effects (demonstrating that improved transmission efficiency increased exposure; Shearer & Ezenwa, 2020).

Although advanced modelling approaches often help in identifying and untangling exposure and susceptibility effects, they nevertheless have limitations. Most importantly, causality is inherently difficult to identify in observational systems, and relies on testing rigorous a priori hypotheses. Even with a well-specified model and accurate empirical measurements, it may be very difficult to conclusively state that exposure or susceptibility is responsible for a given change in burden without experimental manipulation; fully observational studies may be able to state that a given pattern 'conforms to expectations', but without conclusively identifying the underlying mechanisms. For example, a recent study in Soay sheep found that reproductive females experience a peak of strongyle abundance in spring followed by a decline into summer compared to males who showed later peaks in the summer (Sweeny et al., 2022). Although this spring peak for females is expected due to relaxed immunity (Hayward et al., 2018), due to the observational nature of the data it is unclear whether varied peaks for male and females are due primarily to susceptibility, exposure or a combination of both processes (Sweeny et al., 2022).

**Methodological case study: Helminth reinfection in barbary macaques**. Presenting a prime example of all three of our methodological approaches, Müller-Klein et al. (2019) investigated reinfection with gastrointestinal helminths in semi-wild Barbary macaques *Macaca sylvanus*. They first experimentally treated individuals to remove active parasite infections, and then sampled a selection of individuals for faecal egg counts (to approximate infection) and immunophysiological markers (to represent variation in susceptibility), alongside space use and direct interaction networks (to represent exposure risk). Their analysis, which included both classical linear models and patch occupancy models, revealed environmentally and behaviourally mediated effects of both susceptibility and exposure on subsequent helminth reinfection (Müller-Klein et al., 2019). This example serves to illustrate the fine-scale and detailed insight that can be lent by consideration of exposure and susceptibility in observational systems, using experimental manipulation, measurement of multiple explanatory traits and sophisticated modelling approaches.

## 4 | FUTURE DIRECTIONS

Given this depth and breadth of prior understanding, where could the future study of exposure and susceptibility lead? Below, we discuss ongoing frontiers in this area, including application of the Twin Pillar Framework to epidemiology, expansion to consider coinfection with multiple parasites, and further investigation of components of exposure, susceptibility and other within-host processes.

### 4A. Applying the Twin Pillar Framework to epidemiology

Individuals that contribute disproportionately to transmission of parasites in a host population are often known as 'superspreaders' (Lloyd-Smith et al., 2005). Such 'keystone hosts' can influence epidemiological dynamics through many routes, and the roles of hosts' susceptibility and exposure in defining these categories provide additional insights when considered separately (Hawley et al., 2011; Martin et al., 2019; VanderWaal & Ezenwa, 2016). The various forms of keystone hosts (e.g. super-susceptibles, super-contacters and super-receivers) have important epidemiological implications for pathogen fitness ($R_0$), but it is unclear how susceptibility and exposure compare in shaping the distribution of between-individual transmission propensity in a population. Further mechanistic understanding of these processes, followed by inclusion of both in epidemiological frameworks, will contribute to understanding heterogeneity in disease across populations.

Similarly, susceptibility is poorly understood for many novel and emerging human infections. Under accelerating global change, substantial modelling efforts are being devoted to predicting how hosts, pathogens and vectors will shift distributions (e.g. Carlson et al., 2020; Ryan et al., 2019). These approaches often classify risk according to the number of hosts that will be exposed to the new pathogen under changing environmental conditions. However, some studies also implicitly acknowledge susceptibility: for example, when modelling the movement of *Aedes*-borne pathogens, Ryan et al. (2019) highlight that impacts on naive populations may be considerably worse than increased exposure in non-naive populations due to their susceptibility. Future studies that project shifting disease distributions will benefit from including susceptibility in their forecasting framework explicitly: for example, if soil-transmitted helminths shift distributions with climate envelopes, taking into account nutritional status of the newly exposed human populations may be vital when calculating likely public health impacts (Koski & Scott, 2001). Given that global change-associated changes in temperature, food availability and pollution are likely to have considerable ramifications for immunity in wildlife and humans (Becker et al., 2020), understanding susceptibility effects will be more important than ever.

### 4B. Inclusion of susceptibility and exposure to multiple parasites

Coinfection with multiple parasites is the norm in wild populations (Pedersen & Fenton, 2007), and parasites can interact within hosts either directly (via competition for space or resources) or indirectly (via immune-mediated mechanisms). Such interactions can have profound consequences for susceptibility to the parasite of interest (Ezenwa & Jolles, 2015; Knowles et al., 2013), and in some cases can be as important to epidemiological dynamics as host or environmental factors (Telfer et al., 2010). Indeed, it has been suggested

that coinfection can itself be used as a marker or measure of susceptibility; Müller-Klein et al. (2019) found in barbary macaques that coinfection status as a predictor of susceptibility had a similar effect on helminth infection to measures of exposure. However, parasite communities in the wild are rarely monitored holistically, so missing information may regularly be shaping observed patterns. Tractable laboratory systems of coinfection with controlled exposure have provided insight into the mechanisms of interactions observed in the wild (Budischak et al., 2015; Clerc et al., 2019). For example, infection with one pathogen may prime the immune system, affording more effective resistance to the second (Tate, 2019), so that coinfection has protective effects through exposure. Similarly, behavioural disease avoidance is rarely specific to one parasite, and relies more on generalised avoidance of, for example, carcasses or excreta (Weinstein et al., 2018), which could lead to incidental avoidance of other parasites; where parasites have very different patterns in space, it may be difficult to avoid all of them, so avoidance of different parasites could trade-off with each other, potentially mediated by variation in susceptibility (Albery, Newman, et al., 2020). Avoidance and resistance may be (anti-) correlated, so susceptibility and exposure could also be correlated across parasite species (Klemme et al., 2020; Klemme & Karvonen, 2017). As such, coinfecting parasites may have complex, nonlinear impacts on susceptibility and exposure to other parasites in ways that are only beginning to be explored (Gorsich et al., 2014), but which can have significant impacts on wildlife health and disease emergence (Sweeny, Albery, et al., 2021). Investigating these multivariate axes of susceptibility and exposure could unpick how behaviour and immunity have evolved together under the pressure of multiple parasites.

## 4C. Decomposing within-host processes in more host–parasite systems

As outlined above, susceptibility and exposure are both highly multivariate concepts. Isolation of within-host processes that contribute to susceptibility into distinct steps is an invaluable means for identifying relative contributions of exposure and susceptibility to disease dynamics. For example, studies in highly tractable systems such as the crustacean *Daphnia* and its parasites have decomposed the infection process into unique components which are variable among hosts and environments (Hall & Ebert, 2012; Stewart Merrill et al., 2021). Decomposing susceptibility and exposure themselves in this way is epidemiologically important in *Daphnia* and impacts predicted transmission consequences (Stewart Merrill et al., 2021). In the coming years, following from the increasing appreciation and delineation of exposure and susceptibility, we hope that more studies will incorporate between-individual or between-population variation in specific subsets of susceptibility (e.g. invasion vs. cellular compatibility) or exposure (e.g. pathogen encounter rate vs. dose per encounter), particularly combined with other epidemiologically important processes like within-host proliferation and infectiousness. For example, tolerance (i.e. the ability to withstand increasing parasite counts without losing fitness; Råberg et al., 2009) is increasingly appreciated as a vital function of the immune system, and individuals that are more tolerant may appear to be more susceptible if fitness is not taken into account. Quantifying variation in tolerance across individuals within a population, and effectively delineating it from resistance, is a part of a growing number of studies in disease ecology (e.g. Adelman & Hawley, 2017; Burgan et al., 2019; Hayward et al., 2014; Klemme et al., 2020).

Explicitly measuring both exposure and susceptibility and decomposing them into their constituent parts across more systems will produce exciting and mechanistically revealing results. This exercise could ultimately contribute to greater transdisciplinary integration of immunology with disease ecology, and then encourage their ongoing integration with broader ecological fields such as movement ecology (Dougherty et al., 2018; Hawley & Altizer, 2011; Martin et al., 2006). As well as moving us towards a deeper understanding of fundamental ecological processes, this endeavour could lead to more accurate and representative epidemiological models for use in conservation and public health.

### ACKNOWLEDGEMENTS

We thank Daniel Becker and Adam Hayward for their insightful comments. A.R.S. is supported by a large NERC (Grant Number: NE/R016801/1). G.F.A. was supported by a College for Life Sciences Fellowship from the Wissenschaftskolleg zu Berlin.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHORS' CONTRIBUTIONS

G.F.A. and A.R.S. conceived of the framework and wrote the manuscript.

### DATA AVAILABILITY STATEMENT

No data were used for this manuscript.

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**How to cite this article:** Sweeny, A. R. & Albery, G. F. (2022). Exposure and susceptibility: The Twin Pillars of infection. *Functional Ecology*, *00*, 1–14. https://doi.org/10.1111/1365-2435.14065