# Density dependence and disease dynamics: moving towards a predictive framework

Gregory F Albery[1, 2]

1. Wissenschaftskolleg zu Berlin, Berlin, Germany
2. Department of Biology, Georgetown University, Washington, DC, USA

## Abstract

High population density is thought to exacerbate parasite exposure rates, leading to increased transmission and greater disease burdens. Different types of interactions exhibit different relationships with density, and therefore so do parasites that are spread by these interactions. Epidemiological models often assume a given density-transmission relationship, and the validity of this assumption impacts the accuracy of a model's predictions. Despite its foundational relevance to epidemiology and disease ecology, density-transmission functions are generally identified *post hoc* rather than being predictable in advance. Developing a framework for predicting the shape and slope of these relationships could expedite epidemiological responses and improve ecological understanding. Such a framework must allow for both positive and negative correlations between density and infection, originating from non-linear changes in exposure, susceptibility, and a range of other confounders. Here, I argue that a general predictive framework is possible, built "bottom-up" from analyses of spatial and social behaviours. To lay the foundation, I define density dependence according to both spatial and social dimensions of behaviour, I present a series of challenges to address, and I outline a coherent integrative framework to conceptualise and understand density dependence of infection. Finally, I present suggestions for future work, including the collection, mining, and collation of cross-system behavioural and infection data, and experimental approaches that would allow us to extricate density's effects from those of population size and a range of other confounders. Implementing these investigations may allow us to anticipate the epidemiological properties of a wide range of known and unknown parasites, as well as informing the uncertain future of human and animal disease in a rapidly changing and ever-densifying world.

**Keywords**: Disease ecology, Epidemiology, Parasite transmission, Disease dynamics, Density dependence, Behaviour, Spatial analysis, Social networks, Predictive modelling

# Contents

# 0. Introduction

Identifying how population structure and behaviour drive disease dynamics is vital for understanding the demography of natural populations (Tompkins & Begon 1999; Nunn *et al.* 2015a; Silk *et al.* 2019) and the evolution of sociality (Altizer *et al.* 2003; Kappeler *et al.* 2015; Ezenwa *et al.* 2016; Snyder-Mackler *et al.* 2020; Hart & Hart 2021). The world is changing at an unprecedented rate, and animal societies within it (Fisher *et al.* 2021a), and these changes are likely to have complex consequences for the maintenance of disease and the emergence of novel parasites (Gibb *et al.* 2020; Townsend *et al.* 2020; Albery *et al.* 2021a; Fisher *et al.* 2021a; Wang *et al.* 2021). A fundamental paradigm in disease ecology states that individuals living in areas of high local population density (i.e. individuals per unit of space; hereafter, "density") will contact other individuals more often, so they are more often exposed to parasites (i.e., "density-dependent transmission" (McCallum *et al.* 2001; Lloyd-Smith *et al.* 2005; Wilson & Cotter 2009; Hopkins *et al.* 2020)). Parasites that spread via different interactions (defined as an event that might spread a pathogen -- e.g. direct contact, respiratory droplets, or indirect space sharing) are expected to vary in their relationships with host density: some will be positive, as expected, with linear, exponential, or sigmoidal relationships (Figure 1), while those that exhibit no relationship with host density are considered "frequency-dependent" or "density-independent" (Wilson & Cotter 2009; Hopkins *et al.* 2020), and some can in fact be negatively correlated with density (Buck *et al.* 2017; Albery *et al.* 2020). Although frequency dependence and density dependence are often posed as a dichotomy, many density-transmission functions occur somewhere on a continuum between these extremes (Antonovics *et al.* 1995; Ryder *et al.* 2007; Smith *et al.* 2009; Borremans *et al.* 2017b), and considerable research effort is invested in discovering how host density drives infection rates for a range of parasites (reviewed in (Hopkins *et al.* 2020)).

Understanding density-infection relationships is important for several reasons: First, greater parasite exposure is expected to be a primary cost of living in dense social groups (Cote & Poulin 1995; Altizer *et al.* 2003; Poulin & Filion 2021), and the benefits of group living may directly counteract this cost (Almberg *et al.* 2015). A deeper understanding of how density covaries with social connectedness and infection could therefore inform how complex social systems have evolved in spite of (or because of) disease-related costs (Altizer *et al.* 2003; Kappeler *et al.* 2015; Meunier 2015; Ezenwa *et al.* 2016; Hart & Hart 2021). Second, density dependence is a fundamental assumption of many epidemiological models, and fitting inaccurate density-transmission functions risks making inaccurate predictions or drawing unfounded conclusions (McCallum *et al.* 2001; Lloyd-Smith *et al.* 2005; Hopkins *et al.* 2020). Different density-transmission relationships can produce fundamentally different expectations for a parasite's responses to interventions (McCallum *et al.* 2001) and global change (e.g. (Wang *et al.* 2021)), and therefore the success of many modelling-driven interventions ultimately rests on the accuracy of the chosen function. Third, human population density is quickly increasing, especially in urban areas: human population is projected to reach 10 billion by the latter half of the 21$^{st}$ century (United Nations Department of Economic Affairs 2019); wild areas are being converted to human-inhabited land at unprecedented rates, with urban population size and land cover projected to increase substantially (Chen *et al.* 2020; Gao & O'Neill 2020); and dense cohabitation is likely to become increasingly important for living sustainably (Goldstein *et al.* 2020). Predicting density's impacts on disease burdens across multiple scales in the near future should therefore be an important public health priority. Finally, novel parasites are emerging in human populations from wild and domestic animals at increasing rates, posing a substantial threat to human health (Woolhouse & Gowtage-Sequeria 2005; Jones *et al.* 2008; Gibb *et al.* 2020). Many of these parasites are poorly understood prior to their emergence, which reduces our ability to anticipate their epidemiological properties once they have

emerged; being able to predict their relationships with density for use in epidemiological modelling could therefore greatly benefit public health responses.

Despite its foundational relevance to disease ecology and epidemiology, the density dependence of a given parasite is generally assessed *post hoc* rather than being predictable *a priori*. This inherently slows epidemiological responses and inhibits our empirical understanding of the drivers of infection, while introducing uncertainty into the future of disease on a rapidly densifying planet. For example, researchers successfully fitted a saturating density-dependent transmission curve to SARS-CoV-2 by September 2020, 6 months after the pandemic reached the UK (Nightingale *et al.* 2020). SARS-CoV-2 is the most intensely studied parasite in history, with an enormous volume of available data, and therefore likely forms an upper bound for the potential speed of *post hoc* understanding. In other cases, questions about a given parasite's density dependence have been debated for decades: for example, rabies transmission in dogs appears to conform to neither frequency-dependent nor density-dependent models of transmission, hampering control efforts (Morters *et al.* 2013; Townsend *et al.* 2013; Rajeev *et al.* 2020). This lack of predictive capacity has prevailed despite the advent of broadly useful tools for analysing disease dynamics like spatial and social network analysis (Craft 2015; White *et al.* 2017; Albery *et al.* 2021a), the wider availability of behavioural information through GPS tracking and biologging (Kays *et al.* 2015; Smith & Pinter-Wollman 2021), and the profound growth in understanding of transmission dynamics for a range of specific parasites (Hopkins *et al.* 2020). Given our deepening understanding of how spatial behaviour drives the formation of social connections and *vice versa* (Firth & Sheldon 2016; Spiegel *et al.* 2016; Peignier *et al.* 2019), we may be able to identify how density alters behaviours, and therefore exposure rates, across a range of systems. Combined with an understanding of how exposures lead to infections, this information would allow us to model (i.e., predict) density dependence from a generative, "bottom-up" perspective, rather than identifying it from "top-down" demographic data. Already, this approach has been used to great effect in single systems (Borremans *et al.* 2017a). While predicting density-transmission functions in novel systems may seem a lofty goal, it is one worth pursuing; even identifying simple "first principles" rules that govern the shape or slope of such functions could be extremely useful for modelling novel host-pathogen systems about which we have relatively little information.

Here, I argue that developing a predictive framework for density dependence is indeed possible, and requires answering two central questions. First, **"how does adding more individuals in space alter interaction frequency?"** Currently, much evidence for density-infection relationships is indirect, being either: i) mechanism-agnostic and phenomenological; ii) based on purely social metrics like group size, which are potentially unrelated to population density; or iii) based on experimental designs that alter population size alongside population density, such that the two are difficult to extricate. Much evidence in fact examines disease-related impacts of interaction frequency rather than density, while struggling to account for spatially distributed confounders. Directly modelling both spatial and social behaviour at the individual level could ameliorate these problems. Second, **"how do density-related changes in exposure translate to realised changes in infection?"** Historically the problem has mainly considered variation in interaction rates, with less research focussed on how density alters susceptibility to infection. Answering this question will be important for determining the downstream impacts of changes in density and contact rate, which could otherwise be counteracted.

To help move us towards this predictive framework, I discuss how density affects the transmission and maintenance of disease in humans and animals. 1) I define density dependence in terms of both spatial and social dimensions of behaviour, and discuss the evidence base that could be used to broadly predict

density-infection relationships. 2) I identify the questions that we should answer to help build our perspective on density dependence, providing examples for where novel spatial-social approaches may be helpful. 3) I provide a novel framework for conceptualising and testing density effects in disease ecology. I clarify how density should drive interaction rates, and therefore the transmission of parasites, across a range of different interaction types and transmission modes; I further elaborate on density-dependent trends that could affect disease in complex ways, including a series of impacts on susceptibility and other downstream disease processes. 4) Finally, I provide open questions and a series of empirical and theoretical approaches to inform our view of density-dependent disease dynamics in the future. Ultimately, I hope to provide a framework for future investigations, laying the groundwork for predictive models of density dependence in novel and existing host-parasite systems.

# 1. Defining density dependence

In general terms, density refers to a concentration of entities in a defined space, and greater density requires more individuals per unit of space. For this reason, metrics of "population density" must be expressed as "social divided by spatial": for example, "individuals per $km^2$" (McCallum *et al.* 2001; Begon *et al.* 2002; Hu *et al.* 2013). Density can be conceptualised by envisioning interacting individuals as molecules of gas moving in a chamber (Figure 2A-C). Simulations of phenomena like these are sometimes used to examine contact networks and transmission dynamics (e.g. (Hu *et al.* 2013; Pinter-Wollman 2015)); as with a gas, making the chamber smaller, or increasing the number of molecules, increases the rate at which molecules encounter each other (i.e., interact). If these interactions can spread parasites, creating a higher-density population will favour parasite transmission on a *per capita* basis – i.e., each individual has greater exposure, rather than merely increasing exposure rate of the population as a whole – resulting in a greater proportion of infected individuals (Begon *et al.* 2002). Density-dependent transmission functions (Figure 1) examine how increasing density (i.e., adding more individuals per space) affects parasite transmission via altered interaction rates; here defined as the rate at which individuals encounter one another or environmental parasites.

Importantly, "network density" is used in network science to mean "the number of edges present in the network as a proportion of the total number of potential edges" (Sosa *et al.* 2020). Contact network density should correlate positively with transmission probability (and with population density if the contact-relevant interactions are density-dependent), but opting not to specify which "density" is being discussed in a given scenario could lead to confusion regarding a parasite's density dependence, and should be clarified where possible in social-spatial analyses.

Density-independent parasites, meanwhile, are spread by interactions that do not become increasingly common with density (Figure 1), but with absolute numbers of exposure opportunities: interactions like copulation events, for example (Antonovics *et al.* 1995; Lloyd-Smith *et al.* 2004, 2005). Therefore density-independent transmission is expected to correlate with population size rather than population density (Lloyd-Smith *et al.* 2005; Hopkins *et al.* 2020). This phenomenon is also known as "frequency dependence"; however, all parasites are dependent on the frequency of the interactions that spread them, and therefore all parasites are technically "frequency dependent". To avoid any confusion on this front, I use "density dependent" and "density independent" to discuss these cases, but I focus primarily on variation in the slope of the relationship, rather than on whether a parasite falls along a continuum from one to the other (see Section 2A). Importantly, it is often expected that increasing population size will increase density, but size and density can scale idiosyncratically (e.g. (Lunn *et al.* 2021)), so this is not necessarily true.

In ecology and animal behaviour, individuals' movement patterns are unlikely to follow ideal gas laws (Begon *et al.* 2002; Hu *et al.* 2013): for example, if individuals are territorial or avoid each other, adding more individuals to the same space or reducing the habitat area may not increase the probability of interactions/collisions (Figure 2D-F). In these cases, many interaction types will not show a simple relationship with density. Animals can moderate their spatial behaviours independent of their social behaviours, and *vice versa*, or the two may interact – for example, where animals use social cues to determine their movement in space (Firth & Sheldon 2016; Spiegel *et al.* 2016; Peignier *et al.* 2019). Social behaviours alone therefore may not accurately represent density, particularly when modelling the interactions required for parasite transmission (Albery *et al.* 2021a). For example, although group size is often used as a proxy for density, if larger groups increase their ranging area linearly (or if group size linearly responds to the available ranging area), group size will in fact have a flat relationship with density; consequently, group size may not be informative concerning a disease's density dependence. The reverse may also be true: for example, hantavirus transmission does not scale with density in bank voles (*Myodes glareolus*) because individuals reduce the size of their home ranges under higher-density conditions (Reijniers *et al.* 2020). Similar ranging-density relationships have also been demonstrated among leopards (Roex & Balme 2021) and foxes (Sanchez & Hudgens 2015). These complexities, among others, accentuate the need to consider spatial context when examining density's effects on infection.

## A. The evidence for density dependence

Accurately predicting density dependent trends will necessitate drawing on the extensive density dependence literature, which may require harmonising a variety of analytical and experimental approaches. Many studies have examined population-level epidemiological trends associated with specific parasites, verifying to what degree their dynamics align with the expectations of density-dependent transmission models (extensively reviewed in (Hopkins *et al.* 2020)). Their findings have identified a mix of different density-infection functions, and plenty found no evidence for any relationship (e.g. (Ebert *et al.* 2000)). Other studies have empirically correlated density with infection, with a similarly mixed bag of findings (e.g. (Fong 2016)).

Building a successful predictive framework will require cross-system syntheses that allow formal comparisons across systems and the identification of general rules. However, to date, all sufficiently broad analyses have investigated purely social metrics like group size or social connectedness, which do not explicitly consider spatial dimensions of behaviour (Table 1). Earlier examples either compared across multiple species and correlated their social structures with parasitism (Ezenwa 2004; Poulin & Filion 2021), simulated (Nunn *et al.* 2015b), or meta-analysed within-species estimates of group size effects (Cote & Poulin 1995; Rifkin *et al.* 2012; Patterson & Ruckstuhl 2013). More recently, with the growing popularity of network analysis in disease ecology (Craft 2015; White *et al.* 2017; Albery *et al.* 2021a), meta-analyses have targeted social network studies to examine how individual-level sociality drives infection across a range of different systems (Lucatelli *et al.* 2020; Briard & Ezenwa 2021). Ultimately, if density drives greater social connectedness, the findings of these studies may be indicative of density dependent transmission; in fact, in species whose inhabited area grows in step with population size, social connectedness may be a more informative measure of transmission than density (Elliot & Hart 2010). While most earlier analyses mention density, at least to some extent (Cote & Poulin 1995; Rifkin *et al.* 2012; Patterson & Ruckstuhl 2013; Nunn *et al.* 2015b), the more recent social network structure meta-analyses do not (Lucatelli *et al.* 2020; Briard & Ezenwa 2021). This may imply that social drivers of disease are increasingly being distinguished from density dependence.

Several of these studies (Table 1) either fitted transmission mode as an explanatory variable in their meta-analyses, or investigated different transmission modes using separate models to find different results (Cote & Poulin 1995; Rifkin *et al.* 2012; Patterson & Ruckstuhl 2013; Briard & Ezenwa 2021). These models produced some evidence that the effects of sociality differ across parasites of different transmission modes, but findings have varied substantially across studies. For example, (Cote & Poulin 1995) found a positive effect for contagious parasites but a negative trend with mobile parasites; (Rifkin *et al.* 2012) found positive effects for all transmission modes except searching parasites; and (Briard & Ezenwa 2021) found no evidence for variation among transmission modes.

This evidence base is therefore substantial and extremely varied, with some contradictory results. For example, a recent study of coccidia infection in carrion crows (*Corvus corone*) found no effect of social network metrics, but a significant positive effect of group size (Wascher 2021). Finding that group size explained more variation than social structure metrics disagrees with the expectations from the meta-analyses (Lucatelli *et al.* 2020), and the study itself disagreed with earlier findings in the same species (Wascher *et al.* 2019). Moreover, many individual studies find context-dependent effects: for example, a recent analysis of Buggy Creek virus (BCRV) in swallows found positive group size effects in monospecific groups and negative group size effects in mixed flocks (Moore *et al.* 2021). This substantial between-system and between-study variation is a testament to the complexity of sociality-disease relationships, and implies that there is plenty of testable variation in these relationships that might be explained by between-system differences.

## B. Mechanisms that might complicate density effects on infection

Importantly, density can covary with or provoke a number of processes, potentially unlinked to interaction and transmission rates. If unaccounted for, these mechanisms could complicate observed density effects. Here, I briefly outline a selection of such processes, identifying the route via which they might occur and the potential direction of the effect (**+/-** in brackets). $^{S}$ denotes susceptibility-mediated processes; $^{E}$ denotes exposure-mediated processes. This list expands on our previously published framework outlining potential drivers of negative density dependence (Albery *et al.* 2020).

Upstream (pre-exposure) effects include:

1. **Avoidance $^{E}$ (-)**: Individuals can avoid infected conspecifics (Poirotte *et al.* 2017) or parasites in the environment, such that the emergent society is structured and concentrated in areas of lowest disease risk (Weinstein *et al.* 2018; Albery *et al.* 2020).
2. **Condition $^{S}$ (-)**: Habitat selection behaviours draw individuals to areas with abundant resources, providing better nutrition, stronger immunity, and therefore reduced disease burdens.
3. **Competition $^{S}$ (+)**: More individuals in the same area may compete for the available resources, resulting in worse condition and weaker immunity (e.g. (Svensson *et al.* 2001)).
4. **Density-dependent prophylaxis $^{S}$ (-)**: Immunity is preferentially induced or upregulated in high-density contexts, pre-empting increased exposure and preventing infection. This upregulation may be dependent on viewing a sick individual (e.g. (Love *et al.* 2021)).

Downstream (post-exposure) effects include:

5. **Fitness costs (-)**: Parasites cause mortality, reducing host density in highly diseased areas.
6. **Cooperation $^{S\,E}$ (-)**: Hosts at high densities have more partners to cooperate with, either reducing their disease burden directly (e.g. through grooming (Stewart & Macdonald 2003) or

allosuckling (Roulin & Heeb 1999)) or indirectly (e.g. through group hunting benefits (Almberg *et al.* 2015)). They may also provide beneficial microbes that prevent colonisation by parasites (Sassone-Corsi & Raffatellu 2015).

7. **Ostracism [E] (-)**: Highly parasitized individuals altruistically self-remove (e.g. (Rueppell *et al.* 2010)), or are ostracised or murdered by their conspecifics (e.g. (Baracchi *et al.* 2012)). This decreases density in areas that are more highly parasitized. Similar to avoidance but occurs post-infection.
8. **Infection-induced behaviour changes (-)**: Parasitised individuals behave differently, move more when infected, or decide to leave areas in which they become highly infected, decreasing density in those areas. Similar to avoidance and ostracism.
9. **Mobile parasite encounter-dilution effects [E] (-)**: Mobile parasites exhibit a constant attack rate in space, which is diluted in high-density areas such that each individual has a lower parasite burden (Mooring & Hart 1992).
10. **Interspecific encounter-dilution effects [E] (-)**: Other species act as the source of transmission of parasites, with interspecific transmission occurring in space. This transmission is then diluted in high-density areas such that each individual has a lower parasite burden, in the same way as encounter-dilution effects (e.g. (Moore *et al.* 2021)).

# 2. Open questions in density dependence studies

Given the current state of knowledge and this array of contravening mechanisms, what do we need to do to begin predicting density-dependent disease dynamics? Here, I discuss seven questions that will help to do so, all of which are important and interesting research frontiers in their own rights. They include: A) considering a range of density- transmission functions; B) incorporating the role of spatial behaviour into density analyses; C) identifying density-dependent interaction functions using behavioural analyses; appreciating density-dependent changes in D) susceptibility effects and E) benefits of sociality; F) expanding the range of available study systems; and G) clarifying the spatial and temporal scale of density effects. To help considering these questions, I have outlined a range of processes that can alter density dependence of infection (Section 1B).

## A. Diversifying density-transmission functions

One important step toward prediction is to appreciate the wide array of potential density-transmission relationships. Historically, "frequency dependent" and "density dependent" parasites were framed as a dichotomy or opposite ends of a single continuum; for example, the two have been modelled as alternative formulations of a Type II function (Antonovics *et al.* 1995). More recently, it has been demonstrated that density-dependent functions can take other shapes that do not fit into this framework, such as sigmoidal curves (Borremans *et al.* 2017a). Consequently, due to the growing revelation that there are many different density-transmission functions to choose from (Figure 1), it has become increasingly important to move beyond this dichotomy (Hu *et al.* 2013; Hopkins *et al.* 2020). Particularly given that positive density trends could be accelerating or sigmoidal (Figure 1), the observed variation that occurs between given "density-dependent" systems could be greater than the difference between such a "density-dependent" system and a flat "frequency-dependent" system; as such, moving beyond the dichotomy to clarify the slope and shape of these relationships can be vital for understanding a system's dynamics (Hu *et al.* 2013; Hopkins *et al.* 2020).

Importantly, all parasites are dependent on the frequency of the interactions that spread them and are therefore strictly "frequency dependent"; the distinction comes where some interactions are dependent

on density, and therefore only parasites spread by these interactions specifically are "density dependent," while frequency dependent parasites could be more accurately described as "*only* frequency dependent". Framing frequency dependent parasites more often as "density independent" (Hopkins *et al.* 2020) might counter this confusion. Frequency dependent parasites are expected to scale with population size but not population density, while density dependent parasites are expected to scale with population density (and with population size if the population remains in an area of the same size, and is therefore related to density). Increasingly modelling density-contact relationships over a wider range of density values (see section G below), may help to clarify this distinction (Hu *et al.* 2013; Hopkins *et al.* 2020), and may buffer for the fact that a sigmoidal relationship can appear exponential or saturating depending on the chosen range of density values (Figure 1, bottom row).

## B. Incorporating spatial behaviour to differentiate frequency and density effects

As detailed above, many synthetic, cross-system approaches have relied on purely social metrics like group size or social network positions. Despite being widely used to great interest, these purely social metrics may not capture the central definition of density as "individuals *per space*", and rather represent network connectedness or contact number. Some studies use the volume of individuals' spatial overlaps or intersections (e.g. (Schauber *et al.* 2007)), which likewise do not represent density *per se* (Hopkins *et al.* 2020). The incomplete approximation to density could reduce their ability to detect density-infection relationships. For example, Rifkin et al. (2012)'s finding of no encounter-dilution effect for mobile parasites could have originated from the use of group size as a metric rather than density. Encounter-dilution effects are predicated on a spatially distributed parasite attack rate, where a given burden of parasites is shared among the numbers of individuals in that space, such that larger groups dilute the threat (Mooring & Hart 1992). Using group size as a proxy for this effect implicitly relies on the idea that the groups are inhabiting similar areas (or at least areas of similar sizes); if larger groups range over larger areas, this proxy might be unable to detect an encounter-dilution effect. Despite the increased sophistication of social network approaches, it is likewise unlikely that they would be able to detect these spatially explicit effects. The same is true of studies that use annual measures of a single population's size (in terms of numbers of individuals): this metric does not offer information on density itself, unless it can be reliably inferred that the population in question is inhabiting an identical enclosed area (Begon *et al.* 2002) – as with some island populations (e.g. the Soay sheep of St Kilda (Wilson *et al.* 2004)). In contrast, repeating similar analyses with spatial density measures (or at least controlling for spatial behaviour or spatial context) might succeed in identifying encounter-dilution effects across systems.

Although much evidence for density dependence emerges from density manipulations in laboratory populations, these methods often result in an in-step manipulation of interaction frequency that may make density dependence difficult to conclusively identify. For example, one of the most interesting density-dependent trends that laboratory populations have revealed is density-dependent prophylaxis (Section 1B; (Wilson & Cotter 2009). In this scenario, greater host densities provoke greater preemptive ("prophylactic") immune responses, such that each individual in the population is better prepared to respond to parasite exposure. Conventionally, experiments to examine density effects like these generally involve increasing the number of individuals in a given space (e.g. (Wilson *et al.* 2002; Cotter *et al.* 2004; Wilson & Graham 2015)), which increases both density and population size (i.e., interaction frequency). It is therefore possible that immune upregulation could be frequency-dependent (i.e., dependent on the absolute number of social contacts) in the same way as frequency-dependent parasite exposure, rather than being density-dependent (i.e., dependent on the number of social contacts per

space). For example, the mere sight of (sick) conspecifics could result in the preemptive upregulation of immunity as it does in canaries (Love *et al.* 2021). Yet, frequency-dependent prophylaxis has never been investigated or discussed (and the phrase returns no results on google), although it has been suggested that density might not be the most appropriate metric to use to detect prophylactic immunity (Elliot & Hart 2010). If true, this mechanism almost certainly wouldn't change the conclusions of investigations into density-dependent prophylaxis, but might produce different predictions for disease dynamics, just as frequency- and density-dependent transmission do.

To investigate how this size-density confounding might influence inferred disease dynamics, it would be interesting to explicitly alter density and population size along separate axes, and then to investigate their impacts on transmission and susceptibility (Figure 3). For example, how does housing 10 individuals in one container compare with housing 100 individuals in an area that is 10x larger (thereby maintaining density, but increasing group size)? How do these findings compare with housing 100 individuals in the smaller area versus 10 individuals in the larger area (thereby modifying density in both cases)? This exercise could be combined with experiments that ask how infection status affects others' immune expression (e.g. (Love *et al.* 2021)), to investigate whether such responses are context-dependent based on perceived disease risk rather than being dependent solely on the number or density of individuals.

Despite the lack of broad, cross-system meta-analyses, some empirical studies have used continuous, within-population density measures to empirically infer density-infection dynamics. One recent analysis in European badgers (*Meles meles*) found negative density effects in a range of parasites (Albery *et al.* 2020), and no trends with social network metrics, indicating that spatially explicit density effects could produce fundamentally different findings in other systems. Similarly, as outlined above, many studies have fitted epidemiological models to longitudinal data on infection prevalence and demography to identify a suite of density dependence functions (e.g. (Smith *et al.* 2009; Mariën *et al.* 2020)). Given the abundance of such studies (Hopkins *et al.* 2020), it may be possible to conduct a formal meta-analysis to begin identifying the determinants of density-transmission functions that they have identified.

## C. Deriving density-dependent interaction functions in behavioural systems

Most epidemiological models use phenomenological or mechanism-agnostic density-dependent interaction curves (Hopkins *et al.* 2018, 2020), rather than empirically identifying how a given interaction rate increases with density. Where researchers know the specific behaviours that allow transmission (space sharing, den sharing, air sharing, direct contact, mating, fighting, etc. (Gilbertson *et al.* 2020; Albery *et al.* 2021a; Briard & Ezenwa 2021)), epidemiological models could be built "from the ground up," based on extrapolating the effect of density on the relevant contact behaviour to predict its effect on transmission. This first-principles framework would require identifying, across a range of systems, how increasing local density affects the rates of these interactions, and using this knowledge to predict density-interaction functions in other systems. For example, it is still unknown whether certain behaviours differ predictably in their slope (e.g. does density increase fighting more rapidly than it does mating?) or their shape (e.g. are certain behaviours more likely to be exponential, linear, or saturating?). Answers to these questions could be surprisingly easy to attain, as analyses that uncover general rules like these are not uncommon: for example, a recent analysis found that group size and interaction number scale super-linearly across animal species (Rocha *et al.* 2021). A similar analysis could examine density-interaction relationships across a range of systems to identify how they adhere to a range of shapes (Figure 1), and what moderates the slope of the relationship.

While several studies have uncovered positive correlations between aspects of sociality and density (Vander Wal *et al.* 2014; Sanchez & Hudgens 2015; Webber & Vander Wal 2020; Albery *et al.* 2021b) and others have correlated spatial and social proximity (e.g. (Robert *et al.* 2012; Sanchez & Hudgens 2015; Firth & Sheldon 2016)), there have been few direct investigations into how density drives interaction frequencies. Studies generally use discretised between-year or between-population variation in population density or size (e.g. (Webber & Vander Wal 2020)), rather than continuous within-population metrics, which often provides too few unique density values to draw a non-linear relationship between density and interaction rate. This is not universally true, and some systems feature sufficient spatiotemporal replication – particularly rodent trapping studies. (Davis *et al.* 2015) offer an notable example in *Microtus agrestis* field voles, where replicates of annual space use networks across multiple sites allowed them to fit reliable and interesting density-interaction curves, while (Borremans *et al.* 2017a) used over 20 years of monthly density estimates for a population of multimammate mice (*Mastomys natalensis*) to fit a sigmoidal density-contact function. In this case, the model was used further in an epidemiological simulation model, supporting the potential value of the "behaviour-up" approach to density modelling (Borremans *et al.* 2017a). Notably, interaction frequencies can depend simultaneously on both overall population size and local population density (e.g. in red deer; (Albery *et al.* 2021b)), so it may be important to fit both in statistical models.

As density increases, many interaction types will become relatively less likely on a *per capita* basis, or even on an *absolute* basis. For example, if a given animal is more likely to copulate in private than in a group, it is possible that adding more individuals per space will make sexual transmission events in that space less probable. Similarly, if there is a risk of cheaters in a population, cooperative events that cost the individual (e.g., grooming or open resource sharing; see Section 2E) could become less likely in an absolute sense at greater densities, which might increase rates of infection. These effects are likely to cause infection to saturate or decrease at higher densities.

Adding complexity, density dependent transmission functions will not necessarily be universal, even for a given host-pathogen system: they will fundamentally depend on the surrounding environment. For example, when considering fine-scale density dependence in humans, it may be reasonable to expect that adding more individuals to a conference centre will result in a linear (or exponential) increase in handshake interactions; however, adding more individuals to the street will not do the same. Similarly, adding more people into the same church during a choral service may result in a steep increase in air sharing (a dynamic that became very important in the SARS-CoV-2 pandemic (Hamner *et al.* 2020)), but the same may not be true of a train carriage or a music festival. Some environments may be more conducive to avoidance behaviours than others, and this may be taken into consideration when selecting a habitat in the first place (Buck *et al.* 2018; Weinstein *et al.* 2018). For example, structurally complex habitats produced greater re-encounter rates in sleepy lizards (*Tiliqua rugosa*; (Leu *et al.* 2016)), and avoiding infected individuals could be more difficult in these complex environments. All these phenomena could drive variation in density's relationship to interaction frequencies among populations and environments, which introduces critical uncertainty into density-transmission functions. As such, understanding these drivers of variation is likely to be critical to building a robust predictive framework that is able to accommodate a range of host-parasite systems.

## D. Considering density-dependent changes in susceptibility as well as exposure

Despite much discussion around how sociality impacts host susceptibility (Almberg *et al.* 2015; Ezenwa *et al.* 2016), it is unclear how density itself correlates with susceptibility, and therefore how density-dependent parasite transmission translates to realised variation in disease burden. This relationship is

important because it determines how density will result in changes in infection rather than just transmission; for example, if density increases susceptibility while also increasing exposure, does burden increase exponentially? As an example, if there are more individuals per area they will likely be competing more for the same resources (Svensson *et al.* 2001; Body *et al.* 2011; Sanchez & Hudgens 2015; Hasik *et al.* 2021) and will therefore likely have worse nutritional states. Because immunity is costly and therefore often relies on having sufficient resources to mount an immune response (Cressler *et al.* 2014; Becker *et al.* 2018; Budischak *et al.* 2018; Pike *et al.* 2019), individuals living in areas of greater density may have weaker immunity (Das *et al.* 2022). Crowding stress can also increase the frequency of aggressive interactions or inhibit immune expression (Collie *et al.* 2020; Edmunds *et al.* 2021), which could drive strong correlations between density and infection without necessarily driving greater interaction rates. As such, these susceptibility effects could (for example) masquerade as density-transmission relationships or make a linear density-transmission function appear exponential.

Alternatively, these effects could counteract each other: for example, individuals living in areas of higher density could have lower susceptibility because they seek out areas of good nutrition, such that the population centres on high-quality areas, and therefore density and infection are negatively correlated through confounding rather than through a causal relationship. There is some evidence that high-quality habitats can be more attractive even if disease is present (Mierzejewski *et al.* 2019), implying that even greater exposure may not be sufficient to prevent aggregation around resource-rich patches. Similar confounders act in human contexts: for example, it is unclear whether SARS-CoV-2 spread quickly through dense urban populations solely due to the density itself, or because these populations were commonly inhabited by vulnerable individuals with low socioeconomic status (Nightingale *et al.* 2020). Negative density dependence could be driven through disease avoidance as well as by habitat selection. Infection's spatial distribution is highly heterogeneous and ultimately depends on a combination of biotic and abiotic drivers (Becker *et al.* 2020; Albery *et al.* 2022). Because disease reduces hosts' fitness, this spatial heterogeneity motivates animals to avoid hotspots of infection (Buck *et al.* 2018; Weinstein *et al.* 2018). If animals select their habitat based on its propensity to support parasite transmission, individuals in high density areas may be observed with few parasites while those in low density areas have more (Albery *et al.* 2020). Such relationships will depend on how animals weigh up nutritional needs against disease threats (Hutchings *et al.* 2006; Buck *et al.* 2018).

Other similar upstream confounders include mortality and changes in behaviour (Section 1B). For example, if disease is spatially distributed and causes mortality or emigration from the highly infested areas, an apparent negative correlation could emerge between density and disease (Albery *et al.* 2020). Accounting for these upstream confounders may be challenging in these systems, potentially requiring a very rich dataset in terms of host demography and behaviour.

## E. Incorporating beneficial aspects of sociality for disease

Sociality comes with it many beneficial interactions that could reduce disease burdens or alleviate their costs (Altizer *et al.* 2003; Kappeler *et al.* 2015; Ezenwa *et al.* 2016; Snyder-Mackler *et al.* 2020; Hart & Hart 2021). Because the frequency of such interactions is likely to correlate with density, such benefits could complicate observed density-infection relationships. These interactions could include beneficial microbe transfer (Sassone-Corsi & Raffatellu 2015; Ubeda *et al.* 2017), grooming (Stewart & Macdonald 2003), or suckling one another's young (Roulin & Heeb 1999), among others. If, for example, grooming interactions scale with density in exactly the same way as direct contact events that spread fleas, and if grooming interactions directly counteract flea burden, fleas may show no relationship with density and get classed as density-independent (despite potentially showing classical density-dependent

transmission). Many of these interactions could act through changes in susceptibility like those detailed in Section D: for example, if microbiota are acquired through social contact (Dill-McFarland *et al.* 2019; Raulo *et al.* 2021) and if those microbiota help protect against colonising parasites (Sassone-Corsi & Raffatellu 2015), social contact could directly increase resistance to infection, producing a density-dependent pattern. Greater density could also confer better cumulative cognitive capacity to apply to disease mitigation: for example, (Mikheev *et al.* 2013) found that larger groups of fish were better at avoiding parasite infection.

Perhaps most importantly, improved foraging efficiency is a prominent benefit of sociality for many species (Silk 2007; Cantor *et al.* 2020) which could likewise ameliorate the costs of disease (Almberg *et al.* 2015); however, this effect will depend on the balance of competition *versus* cooperation in the population and the social system in question, particularly given the effects of crowding stress outlined above (Collie *et al.* 2020; Edmunds *et al.* 2021). As such, understanding how changing density translates to realised changes in infection may require understanding a range of complex and contrasting density trends, for a range of different interactions and susceptibility drivers that are not necessarily related to transmission itself.

## F. Expanding the range of available study systems

Density-transmission relationships may be easier to identify and generalise if we examine them in a larger number of wild systems. In particular, many researchers experimentally manipulate density in the laboratory, compare populations with different social structures, or correlate species-level means for social structures and parasite traits. While these approaches have been practical and highly revealing solutions to answering these questions, a number of difficulties could prevent their findings from being used to build predictive density-transmission functions.

In captive or wild animal populations, density may be directly manipulated by altering the number of individuals that inhabit a given container (e.g. (Raffel *et al.* 2010; Buck *et al.* 2017; Hasik *et al.* 2021)) or by changing the volume of the container itself (e.g. (Modlmeier *et al.* 2019)). This avoids underlying confounders like resource availabilities (Section 1B) more effectively than any other approaches; however, because laboratory environments are by definition restrictive and simplify away these potentially important confounders, they may not accurately approximate wild environments. For example, animals are often able to avoid infected individuals (Poirotte *et al.* 2017; Stroeymeyt *et al.* 2018), food (Moleón *et al.* 2017), faeces (Poirotte & Kappeler 2019), or geographic transmission hotspots (Albery *et al.* 2020), distributing their population in space according to disease risk (Weinstein *et al.* 2018). Confining large numbers of individuals to a small area, such that their movement is artificially restricted, may therefore provide inaccurate insights into parasite transmission in the wild (Figure 2). Similar to the difficulties with experimental manipulations for density-dependent prophylaxis outlined above, these approaches also confound changes in density with changes in population size (see Section 2B), which could be remedied using novel experimental designs (Figure 3).

Some ecological studies examine multiple discrete populations or aggregations of the same host species, where each population has a different size or density (e.g. (Mbora *et al.* 2009; Downs *et al.* 2015; Webber & Vander Wal 2020; Fisher *et al.* 2021b)). Others use the same population but with different population sizes or densities at different times (e.g. annually) (Coltman *et al.* 1999; Body *et al.* 2011). Although experimental manipulations of such populations are promising and evade many of the problems of laboratory populations (e.g. (Mugabo *et al.* 2015; Buck *et al.* 2017; Webber & Vander Wal 2020)), due to operational restrictions multi-population studies often rely on relatively few

replicates – for example, densities are regularly discretised into "high" and "low" (Coltman *et al.* 1999; Fisher *et al.* 2021b) – and in these cases nonlinear relationships may be very difficult to observe. Similarly, as outlined throughout this section, and in Section 1B and Figure 4, density has many covarying confounders that may confuse relationships with infection (Body *et al.* 2011); statistically, the use of several discrete populations reduces a study's ability to identify density effects and distinguish them from the underlying confounders and susceptibility effects (Section 1B). Low replicate numbers like these have long been appreciated as a difficulty investigating density dependence in wild animals (Lloyd-Smith *et al.* 2005). Finally, these populations could suffer from variation in space use in the same way as laboratory populations: if different populations are designated as being at different densities, but the populations use space in very different ways, density effects could be obfuscated (Begon *et al.* 2002).

Finally, between-species comparisons (e.g. (Ezenwa 2004)) may be confounded by coevolutionary processes: in particular, parasites impose selection pressures on social behaviour, so species' social structures may have evolved in response to parasite transmission rather than driving observed variation in burden (Cote & Poulin 1995; Altizer *et al.* 2003; Poulin & Filion 2021). Moreover, summarising these variables at the species levels risks losing resolution and sample size, and may run into similar confounders as the between-population comparisons above. On the positive side, these facts may lend such studies to identifying species-level compensatory social evolution better than others (e.g. (Poulin & Filion 2021)).

All these processes could be complicating links between socio-spatial behaviour and disease in such studies, so that density effects might be difficult to detect. For these reasons, within-population analyses of local population density's effects on behaviour and infection may offer the most power and reliability when identifying density effects (Albery *et al.* 2021a); however, if sufficient replication can be achieved, multiple populations (or long-term observation of the same population) can be highly productive (e.g. (Davis *et al.* 2015; Borremans *et al.* 2017a)).

## G. Clarifying the spatiotemporal scale of density-infection interrelationships

For a predictive framework to be maximally useful, we must also clarify the scale at which density dependence might occur, and be able to predict its effects at a given resolution (Antonovics 2017). Scale-dependent findings are extremely common in disease ecology (Cohen *et al.* 2016; Lachish & Murray 2018; Morand *et al.* 2019), and deciding on the right spatiotemporal sampling scale is likely to be extremely important for detecting density-transmission relationships. For example, transmission may be density-independent within groups but density-dependent between groups (Loehle 1995; Schmid-Hempel 2017; Webber & Vander Wal 2020). Similarly, Morogoro virus correlates positively with the density of multimammate mice (*Mastomys natalensis*), but with a time lag of several months (Mariën *et al.* 2020), so selecting the correct temporal scale is important for successfully identifying a density-dependent effect. The direction and magnitude of these effects will depend intimately on host and parasite traits like movement, reproduction, and mortality.

To illustrate this point, conventional wisdom states that mobile parasites will not correlate positively with density due to the encounter-dilution effect (Section 1B; (Mooring & Hart 1992; Cote & Poulin 1995; Patterson & Ruckstuhl 2013)). However, even mobile parasites cannot exist without *some* hosts to parasitise in the vicinity; as such, at some point of low density, there will be too few hosts for the parasites to survive in a given area, which inherently imposes density dependence on those parasites. That is, at some spatiotemporal scale, even highly mobile parasites *must* be density dependent. As

expected, discovery of encounter-dilution effects does indeed depend on the spatial scale of the investigation (Buck *et al.* 2017). The same may be true at very coarse population scales – for example where large, dense populations of hosts spread over a large area are able to sustain a large number of mobile parasites. Comparing this large population with a smaller population that is less able to sustain the same abundance of parasites could reveal a positive density trend *between* populations, even if an encounter-dilution effect produces a negative density trend *within* populations. Similarly, for mobile parasites that are nevertheless able to reproduce quickly on the population of known hosts (relative to the hosts' movement ability), the resources presented by greater host density could flip the relationship and produce a positive density effect, regardless of the parasite's movement capacity.

Context-dependent density trends are true of other parasite transmission modes: for example, there is some evidence that sexually transmitted parasites are density-dependent at low host densities, but frequency-dependent at high host densities (Hopkins *et al.* 2020). This is a non-linear density relationship, where the slope of the density-transmission relationship changes according to host density (Figure 1). This general problem is especially important when it comes to practical applications of density dependence theory: for fundamental epidemiology, it would be useful to understand not only fine-scale density effects (e.g. "how does adding more individuals to this room affect the probability of an outbreak of airborne parasites") but also broad-scale epidemiological trends (e.g. "will this parasite preferentially break out in densely inhabited cities"). One of the greatest challenges in the onward development of a predictive framework will require bridging these two scales of question to achieve a synthetic predictive framework.

# 3. Moving towards a predictive framework

To summarise, we would benefit from a clearer understanding of some fundamental aspects of density-dependent transmission (how density alters interaction frequency and therefore exposure), as well as the more complex interrelationships (e.g. density's correlations with susceptibility, mortality, or beneficial interactions). Even identification of the general (non-)linearity of different interaction types could form an important fundamental basis to make predictions from. Given these challenges, how do we address the problem of predicting density dependence? Ameliorating these research gaps to build a predictive framework is not an insurmountable task; in fact, it may require relatively few changes to ongoing research directions. This will involve conducting a range of within-population analyses examining how spatial density measures drive interaction frequency alongside either susceptibility or infection, potentially mirrored by experimental manipulations that alter population size and density separately (Figure 3). Ideally, these studies will incorporate density-driven variation in 1) transmission probability and 2) susceptibility to infection, alongside a range of other confounders (Section 1B). These studies should then be meta-analysed to identify how a broad selection of host and parasite factors (e.g. transmission mode, host mobility, and population dynamics) drive variation in density effects across host-parasite systems.

To help conceptualise these interrelationships, I summarise the steps from initial contact through to onward transmission for infection with a given parasite, including the effects of environment, spatial behaviour, and density (Figure 4). Regardless of host traits (e.g. social system, mobility, or life history) or parasite traits (e.g. transmission mode, taxon, or life cycle), there are certain necessary universal traits of a predictive framework, which must include identifying 1) how density will alter the rate of a given interaction that drives parasite exposure, and 2) how density will covary with other processes

that could change the outcome of this exposure (i.e., whether it results in a successful infection, and if so what the intensity of infection will be).

Host individuals have home ranges, within which they move. If two individuals' home ranges overlap, they may interact indirectly; if they overlap in space at the same time, they can interact directly. Adding more individuals into the same space (or reducing the size of the space) generally makes these interactions more likely, but this relationship is more strongly positive for some interactions (e.g. air sharing) than for others (e.g. copulation events) and uncertain or intermediate for some (e.g. handshakes). How these interactions change with density could depend on the spatial behaviours of the population (e.g. avoidance or territoriality), and often a given interaction's relationship with density will depend on the location itself. For example, air sharing in a plane cabin will be highly sensitive to the density of people in the cabin, while air sharing in an open field will be far less density-dependent. Similarly, copulation events may be more density-dependent in mating grounds than elsewhere in the species' habitat. More subtly, handshakes may be more density-dependent at a conference than in the street.

The above covers density-dependent *transmission*; where we are interested in density-dependent *infection*, susceptibility and other within-host processes must be considered. All else being equal, we expect positive density dependence of infection when density increases the frequency of interactions that spread parasites, or of interactions that are disadvantageous in other ways (and which therefore increase the probability of successful transmission following an exposure event); for example, greater competition for the available resources or more aggressive interactions leading to stress, both of which could weaken parasite resistance. In contrast, we expect negative density dependence when density correlates with beneficial between-individual interactions that increase parasite resistance (e.g. grooming or microbe transfer) or alleviate the costs (e.g. improved resource acquisition); when behavioural mechanisms can reduce exposure to parasites and produce negative density correlations (e.g. avoidance, murder, or ostracism); or when population density is correlated with other traits that increase immune resistance and therefore reduce infection (e.g. resource availability). Alternatively, greater mortality in highly parasitised areas may *create* a negative density trend. Finally, encounter-dilution effects could create negative density trends by dividing a given local burden of parasites among the available hosts, faster than they can reproduce on those costs. The outcome of changes in density for disease will depend on the balance of all these processes at the chosen spatiotemporal scale.

# 4. Future work

Practically, a range of empirical approaches could contribute to delivering this framework. First, the evidence base could benefit from a wider variety of empirical analyses that control for the confounders I have outlined here. These could involve more spatial density metrics and within-population analyses, and large population-level analyses, across a wider variety of systems. The growth in spatial and social network analyses in disease ecology will contribute to this task (Craft 2015; White *et al.* 2017; Albery *et al.* 2021a), as will the use of biologging approaches that produce large datasets of behavioural data (Kays *et al.* 2015; Smith & Pinter-Wollman 2021). For example, a recent analysis investigated how widespread anthropogenic disturbance altered animal space use using telemetry data from a wide variety of different systems (Doherty *et al.* 2021). The ecological data revolution is becoming particularly fruitful at the intersection of disease and behavioural ecology: disease datasets are now being built up by data mining approaches (Han *et al.* 2020; Poulin *et al.* 2021) and there are a growing number of large, open-source datasets with available host-parasite association or prevalence data (Cohen *et al.*

2020; Gibb *et al.* 2021), as well as widely available behavioural datasets like the animal social network repository (ASNR; (Sah *et al.* 2019)) and demographic datasets like the TetraDENSITY database of vertebrates' population density estimates (Santini *et al.* 2018a). Datasets like these are already being integrated to answer questions at the sociality-disease interface: for example, (Poulin & Filion 2021) combined the global mammal parasite database (GMPD; (Stephens *et al.* 2017)) with the ASNR (Sah *et al.* 2019) to investigate how primate species' social networks might have evolved in response to parasite pressure. Similar data-synthesising approaches will be important in answering the questions I have put forward in this review in a general context, giving us the best possible chance to build a generalisable framework for understanding and predicting density-dependent disease dynamics.

This meta-dataset could be supplemented with further laboratory or captive systems that allow experimental manipulation of densities separate from population sizes, as outlined above and in Figure 3, and/or with experimental investigation of specific immune and behavioural traits. To draw a parallel, a broad GPS-facilitated investigation like (Doherty *et al.* 2021)'s study of anthropogenic noise impacts on disease might be supplemented by experimental investigations of the effects of traffic on *ex situ* immune function (e.g. (Brumm *et al.* 2021)), and the same could be done for density effects both across wild populations and within captive contexts.

When more studies have been carried out and more data collated, newly revisiting large-scale cross-system analyses of social behaviour, and incorporating spatial components, could reveal much about the underlying drivers of density dependence and social costs for disease. So far, large-scale investigations into social drivers of wildlife disease have meta-analysed a range of other studies' effect estimates or conducted species-level comparisons (Table 1). Another approach to meta-analysis involves collecting raw datasets and applying standardised analyses across them, and then meta-analysing the results (e.g. (Albery *et al.* 2022)). Although this approach requires substantial additional data manipulation and analysis, it reduces extraneous variation introduced by methodological differences between modelling approaches, and facilitates the application of specialised approaches. These approaches may include spatial analyses that are relatively rarely applied in disease ecology and ecoimmunology (Becker *et al.* 2020; Albery *et al.* 2021a). Carrying out these high-power analyses may allow us to move between scales, from within-population to between-population to between-species, to resolve the problems of scale dependence outlined in Section 2G, and to anticipate compensatory evolutionary changes in behaviour between species (Altizer *et al.* 2003; Poulin & Filion 2021).

Finally, these findings should be extrapolated to their applied contexts, both in animals and in humans. There are already species-level analyses of the determinants of animals' population density (Santini *et al.* 2018b) and similar species-level model formulations have been used regularly for informing on mammals' zoonotic risk, but without uncovering conclusive roles of population density in driving risk (Olival *et al.* 2017). Carrying out these analyses at within- and between-population levels, supplemented with higher-resolution disease data, might inform the roles of population density in driving zoonotic risk in the future. For example, by combining epidemiological models and species distribution models, (Wang *et al.* 2021) predicted that global change-related changes in mammal community composition will drive a decrease in density-dependent infections in mammals, but an increase in frequency-dependent ones, using a dichotomous formula for the two. A sophisticated generative model for density-infection functions could elaborate on these predictions by introducing variation in the slope and shape of the effects of density.

In humans, ideally, we will be able to examine how adding more individuals to the same rooms, areas, and populations will drive infection with a named parasite based as few traits as possible. As well as

allowing us to build density-dependent transmission functions for use in epidemiological models, developing the framework in an applied context may help to answer some persistent questions; for example, answering whether pathogens spread through urban populations because of greater density, or because these populations are associated with economic deprivation and increased susceptibility (Nightingale *et al.* 2020).

# 5. Conclusions

1. Density dependent parasite transmission is a fundamental parameter in epidemiology and disease ecology, but our tendency to identify density dependence *post hoc* inhibits our understanding of disease dynamics and slows the development of interventions for a given parasite.
2. Much purported evidence for density dependence so far is based on between-population comparisons and social behaviour rather than spatial behaviour, which complicates our identification of density effects *per se*.
3. To better understand and eventually predict density dependence, we could benefit from considering a range of density- transmission functions; incorporating the role of spatial behaviour into density analyses; identifying density-dependent interaction functions using behavioural analyses; appreciating density-dependent changes in susceptibility effects and benefits of sociality; expanding the range of available study systems; and clarifying the spatial and temporal scale of density effects.
4. By incorporating these viewpoints and empirical expansions, we may be able to predict how a given host-pathogen system is going to behave by considering a "bottom-up" approach based on the density dependence of a given behavioural interaction, with density-dependent susceptibility effects considered in addition.
5. Implementing this framework could benefit from the wider availability of open datasets of behaviour and infection. Moving forward, addressing the questions I have presented here will help to further our understanding of the ecology of disease in an ever-densifying world in the coming century.

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## Table 1: Published meta-analyses of sociality-infection relationships

| |
|---|
| (Cote & Poulin 1995) |
| Title: "Parasitism and group size in social animals: a meta-analysis" |
| Data: Meta-analysis of 6 studies of parasite prevalence and 15 studies of parasite intensity. Tested mobile and contagious parasites in separate models. |
| Results: Consistent positive correlations between host group size and prevalence and intensity of contagious parasites. Intensity of infection by mobile parasites consistently decreased as host group size increased. |
| (Ezenwa 2004) |
| Title: "Host social behavior and parasitic infection: A multifactorial approach" |
| Data: Original data concerning gastrointestinal parasite infection rates for 11 ungulate species. |
| Results: Territorial host genera were more likely to be infected with strongyle nematodes than were nonterritorial hosts, and gregarious hosts were more infected than were solitary hosts. |
| (Rifkin *et al.* 2012) |
| Title: "Do animals living in larger groups experience greater parasitism? A meta-analysis" |
| Data: Meta-analysis of 69 studies of the relationship between group size and parasite risk, as measured by parasitism and immune defences. Fitted transmission mode as an explanatory variable. |
| Results: Similar positive effect of group size for all transmission modes except searching (no effect). |
| (Patterson & Ruckstuhl 2013) |
| Title: "Parasite infection and host group size: a meta-analytical review" |
| Data: 70 correlations of parasite prevalence, intensity and species richness with host group size. |
| Results: Parasite intensity and prevalence both correlated with group size. No relationship between host group size and parasite species richness. Mobile parasite intensity correlated negatively with group size of sedentary hosts, but not mobile hosts. |
| (Nunn *et al.* 2015b) |
| Title: "Infectious disease and group size: more than just a numbers game" |
| Data: Meta-analysis of the association between group size and four network structure metrics in 43 vertebrate and invertebrate species. Used a theoretical model to explore the effects of subgrouping on disease spread in socially structured populations. |
| Results: Outbreaks reached higher prevalence when groups were larger, but subgrouping reduced prevalence. Subgrouping also acted as a 'brake' on disease spread between groups. |
| (Briard & Ezenwa 2021) |
| Title: "Parasitism and host social behaviour: a meta-analysis of insights derived from social network analysis" |

| |
|---|
| Data: 210 associations between parasite burden and individual level network metrics extracted from 18 published articles. Included transmission mode (and congruence between transmission mode and social network compilation method) as a covariate. |
| Results: Positive effect of social network metrics on parasite infection at the individual level. Found little evidence for transmission mode effect. |
| (Lucatelli *et al.* 2020) |
| Title: "Social interaction, and not group size, predicts parasite burden in mammals" |
| Data: Meta-analysis of 43 studies examining group size-infection relationships and 32 examining social structure-infection relationships. |
| Results: No relationship between group size and infection; some relationship between social structure and infection. |
| (Poulin & Filion 2021) |
| Title: "Evolution of social behaviour in an infectious world: comparative analysis of social network structure versus parasite richness" |
| Data: Species-level parasite richness data (Stephens *et al.* 2017) and social network structure data from the Animal Social Network Repository (Sah *et al.* 2019). |
| Results: Parasite richness correlates with degree heterogeneity, implying that parasite-related selective pressures have driven the evolution of social network structure. |

Table 1: Previously published cross-system analyses of sociality-infection relationships, in chronological order. NB none of these studies directly investigated density effects (i.e., individuals per unit of space), but some assume that sociality and density are positively correlated.

## Figure 1: Example density-transmission functions

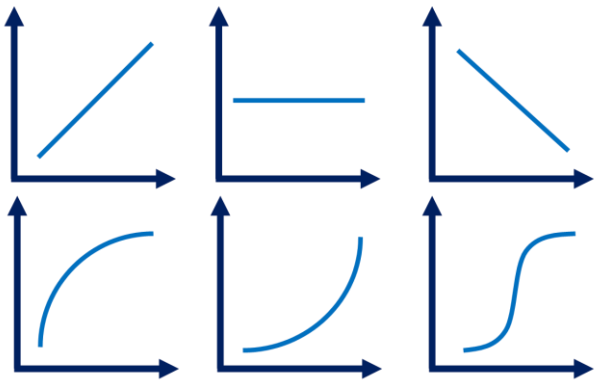

Figure 1: A selection of six simple theoretical relationships between density (X axis) and transmission (Y axis), demonstrating the potential variation in the shape of the relationship (i.e., density-dependent transmission functions). The top row, from left to right, depicts linear increasing, flat, and linear decreasing transmission; the bottom row depicts saturating, exponential, and sigmoidal curves.

## Figure 2: Density, population size, geographic area, and interaction rates

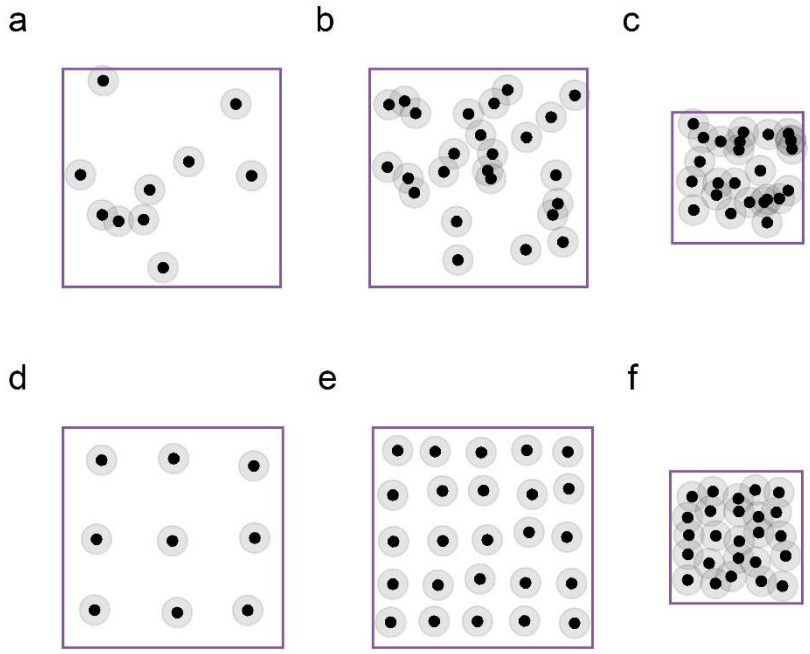


Figure 2: A simulated population's spatial locations, depicting density's relationship to ideal gas laws. In the top row, each individual's location (black dots) is randomly placed within restrictions imposed by the environment (purple box). Each dot has been given a transparent ring to denote an arbitrary interaction distance; two individuals with overlapping rings are taken to be interacting. In panel a), there are 10 individuals. In panel b), there are 25 individuals in the same space, increasing the probability that they will touch (i.e., interact). In panel c), the habitable landscape is smaller, but with the same number of individuals inhabiting it as b), increasing the probability that they will interact. In the bottom row, the population is evenly spaced within the boundaries as a result of individual avoidance behaviours (each individual is attempting to maintain a certain distance from other individuals). This spacing means that adding more individuals to the same space in panel e) does not increase the probability that they will interact, but then making the habitat smaller in addition in panel f) does.

# Figure 3: Experimental designs to extricate density and frequency dependence

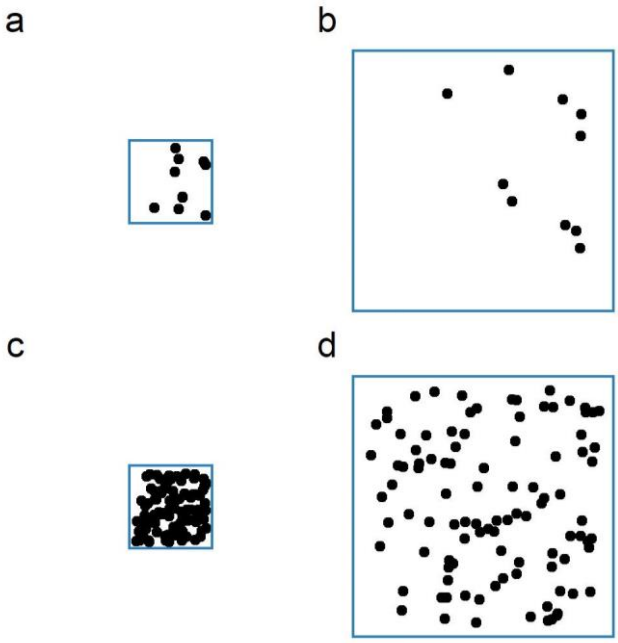


Figure 3: Experimental design can be used to extricate the effects of population size (or interaction frequency) and population density. Panel a) has 10 individuals living in a square with area 10. Panel b) has the same number of individuals living in a square 10x larger (area 100). Panel c) has 100 individuals living in area 10, while panel d) has 100 individuals living in area 100. Both panels a) and d) have a density of one individual per unit area. Therefore, moving between panels a) and b) alters population density without altering population size; moving between panels a) and c) alters population size and population density simultaneously; moving between panels a) and d) alters population size without altering population density. NB in this figure I have displayed two replicates of each, but it would be desirable to modify both dimensions using more than two replicates to produce a continuum of variation.

## Figure 4: Density and disease progression

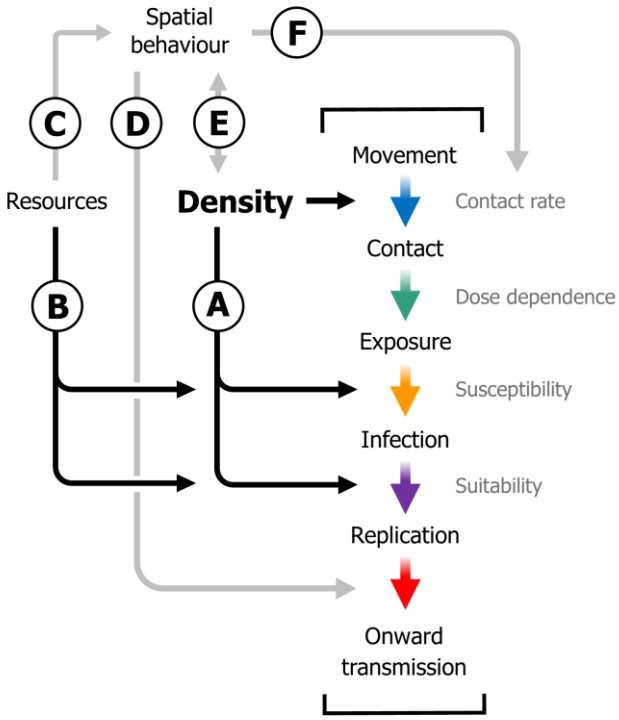


Figure 4: Population density is part of a nexus of interacting processes related to parasite transmission, disease progression, and maintenance. Thick, coloured arrows represent steps along the process of an individual becoming infected with a given parasite. Thin black or grey arrows denote links between environmental resources, spatial behaviours, density, and the coloured steps. The light grey terms next to the coloured arrows name the processes or traits governing transitions between those two stages (e.g. the conversion of movement to encounters is the encounter rate; the transition from encounter to exposure is the dose dependence of the disease). These links are as follows: A) Density affects hosts' susceptibility to the parasites and the parasites' ability to replicate within the hosts ("suitability"), for reasons elaborated upon in Section 1B. B) Resources alter susceptibility and suitability by affecting the immune system; if there are more resources available per individual, each individual's immune system may be more able to resist infection. C) The distribution of resources in the environment defines the distribution of hosts through habitat selection behaviours. D) Spatial behaviour (e.g. location in the environment) determines onward transmission of the parasite because some parasites develop and spread more easily in some environments than others. E) Spatial behaviours determine the density distribution of the hosts, and many spatial behaviours are density- or sociality-dependent, using social cues. F) Spatial behaviours directly influence movement through the environment, and therefore encounter rates.

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