



## REVIEW

# Macroimmunology: The drivers and consequences of spatial patterns in wildlife immune defence

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**Abstract**

1. The prevalence and intensity of parasites in wild hosts varies across space and is a key determinant of infection risk in humans, domestic animals and threatened wildlife. Because the immune system serves as the primary barrier to infection, replication and transmission following exposure, we here consider the environmental drivers of immunity. Spatial variation in parasite pressure, abiotic and biotic conditions, and anthropogenic factors can all shape immunity across spatial scales. Identifying the most important spatial drivers of immunity could help preempt infectious disease risks, especially in the context of how large-scale factors such as urbanization affect defence by changing environmental conditions.
2. We provide a synthesis of how to apply macroecological approaches to the study of ecoimmunology (i.e. macroimmunology). We first review spatial factors that could generate spatial variation in defence, highlighting the need for large-scale studies that can differentiate competing environmental predictors of immunity and detailing contexts where this approach might be favoured over small-scale experimental studies. We next conduct a systematic review of the literature to assess the frequency of spatial studies and to classify them according to taxa, immune measures, spatial replication and extent, and statistical methods.
3. We review 210 ecoimmunology studies sampling multiple host populations. We show that whereas spatial approaches are relatively common, spatial replication is generally low and unlikely to provide sufficient environmental variation or power to differentiate competing spatial hypotheses. We also highlight statistical biases in macroimmunology, in that few studies characterize and account for spatial dependence statistically, potentially affecting inferences for the relationships between environmental conditions and immune defence.
4. We use these findings to describe tools from geostatistics and spatial modelling that can improve inference about the associations between environmental and immunological variation. In particular, we emphasize exploratory tools that can

guide spatial sampling and highlight the need for greater use of mixed-effects models that account for spatial variability while also allowing researchers to account for both individual- and habitat-level covariates.

5. We finally discuss future research priorities for macroimmunology, including focusing on latitudinal gradients, range expansions and urbanization as being especially amenable to large-scale spatial approaches. Methodologically, we highlight critical opportunities posed by assessing spatial variation in host tolerance, using metagenomics to quantify spatial variation in parasite pressure, coupling large-scale field studies with small-scale field experiments and longitudinal approaches, and applying statistical tools from macroecology and meta-analysis to identify generalizable spatial patterns. Such work will facilitate scaling ecoimmunology from individual- to habitat-level insights about the drivers of immune defence and help predict where environmental change may most alter infectious disease risk.

#### KEYWORDS

ecoimmunology, host competence, macroecology, resistance, spatial autocorrelation, zoonoses

## 1 | INTRODUCTION

Emerging infectious diseases threaten wildlife, humans and domestic animals (Plowright et al., 2017; Smith, Acevedo-Whitehouse, & Pedersen, 2009). By serving as primary barrier to infection, replication and transmission following exposure, the host immune system plays a critical role in determining the outcome of these host–parasite interactions (Combes, 2001). Variation in immunity can further produce heterogeneity in traits that govern the population dynamics of infectious disease (Hawley & Altizer, 2011; Jolles, Beechler, & Dolan, 2015). The primary aim of ecoimmunology has accordingly been to explain variation in individual immune phenotypes and to understand their fitness consequences (Graham et al., 2011; Pedersen & Babayan, 2011). However, ecoimmunology increasingly acknowledges how broader evolutionary and ecological contexts shape defence (Becker, Downs, Downs, & Martin, 2019; Schoenle, Downs, & Martin, 2018). Between-population sources of immunological variation are becoming increasingly important to consider in the context of environmental change, as large-scale anthropogenic factors such as urbanization and deforestation are influencing immunity by altering environmental conditions (Acevedo-Whitehouse & Duffus, 2009; Martin, Hopkins, Mydlarz, & Rohr, 2010).



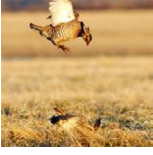



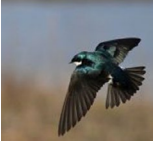

Immune phenotypes are individual characteristics, and the composition of susceptible and resistant hosts in a population determines whether parasites can invade and persist (e.g. herd immunity; Anderson & May, 1991). Individual heterogeneity is shaped not only by the genetic variation of hosts (and parasites) but also by the environment and resultant plasticity: the ability of genotypes to express different phenotypes across environmental contexts (Schmid-Hempel, 2003; West-Eberhard, 2003). These genotype-by-environment interactions highlight the role that

habitat heterogeneity plays in shaping immunity and infection outcomes (Gervasi, Civitello, Kilvitis, & Martin, 2015; Paull et al., 2012). Host genotypes, alongside factors such as nutrition or reproductive status, affect whether an individual in a particular habitat succumbs to infection or lives to transmit to a susceptible host (Plowright, Field, et al., 2008). For example, mathematical models show how resource-rich habitats can homogenize host infectious periods in a population and limit epidemics (Hall, 2019).

Environmental factors operating at multiple spatial scales can drive immunological variation. At least three non-exclusive factors may vary over space and modify immunity (Table 1): (a) spatial variation in parasite pressure that selects for and stimulates immune investment, (b) spatial variation in abiotic conditions and biotic interactions that modify allocation of energy and resources to costly defence and (c) anthropogenic changes that alter either of these factors (e.g. urbanization) or directly alter immunity (e.g. contaminants). These spatial factors commonly act on phenotypic plasticity (e.g. variation in food, temperature), although some can also affect host immunogenetics (e.g. parasite-mediated selection and population isolation via habitat loss).

Such spatial factors are more likely to act in concert, rather than in isolation, to shape immunity. In some cases, captive studies or field manipulations can isolate particular factors and identify causal links with immune phenotypes. These approaches are most relevant when testing predominantly local sources of environmental variation. For example, experimental artificial light at night, an aspect of urban environments, alters immune gene regulatory networks of house sparrows *Passer domesticus* and, in turn, the duration of infectiousness for transmitting West Nile virus to mosquitoes (Kernbach et al., 2019). In addition, common garden approaches can elucidate whether population differences in immunity persist under identical environmental conditions; this

**TABLE 1** Select examples of multi-site studies of ecoimmunology, arranged by the spatial mechanism(s) expected to link environmental variation with immunity: parasite pressure, abiotic and biotic conditions, and anthropogenic factors

Host species <sup>a</sup>	Immune measure	Study design	Spatial mechanism	Association with host immunity	References
 House finch ( <i>Haemorhous mexicanus</i> )	Spleen transcriptome	2 sites, United States	Parasite pressure	Few genes differentially expressed by site exposure history	Zhang, Hill, Edwards, and Backström (2014)
 Bank vole ( <i>Myodes glareolus</i> )	Frequency of TLR2 protective variant	21 sites, across Europe	Parasite pressure	Gene frequency positively associated with human Lyme disease rates	Tschirren (2015)
 Greater prairie chicken ( <i>Tympanuchus cupido</i> )	Non-MHC immune genes	6 sites, central United States	Biotic	Immune gene diversity positively associated with population size	Bollmer, Ruder, Johnson, Eimes, and Dunn (2011)
 Purple sea fan ( <i>Gorgonia ventalina</i> )	Lysozyme-like activity	6 sites, Florida Keys, United States	Abiotic, parasite pressure	Water quality, but not disease prevalence, positively correlated with coral immunity	Couch et al. (2008)
 Freshwater crustacean ( <i>Gammarus pulex</i> )	Phenoloxidase activity (PO)	12 sites, Burgundy, France	Abiotic, parasite pressure	PO negatively associated with water conductivity and prevalence	Cornet et al. (2009)
 European honey bee ( <i>Apis mellifera</i> )	PO, encapsulation response	23 sites, Raleigh, United States	Anthropogenic	Innate immunity not associated with urbanization	Appler, Frank, and Tarpay (2015)
 Tree swallow ( <i>Tachycineta bicolor</i> )	Bacterial killing ability	6 sites, Québec, Canada	Anthropogenic	Birds in more agricultural habitat had stronger bacterial killing ability (BKA)	Schmitt et al. (2017)
 Vampire bat ( <i>Desmodus rotundus</i> )	Bacterial killing ability	10 sites, Latin America	Biotic, anthropogenic	BKA positively associated with demography and livestock	Becker, Czirják, Volokhov, et al. (2018)

Note: We also include the immune parameters measured, aspects of study design (e.g. spatial replication, region) and key findings.

<sup>a</sup>All images from Wikimedia Commons.

allows differentiating genotypic variation from phenotypic plasticity (Bonneaud et al., 2011). However, such experimental efforts may be limited by the number of co-occurring sources of environmental variation that can be factorially varied (e.g. crossing treatments of food, temperature, infection prevalence and population

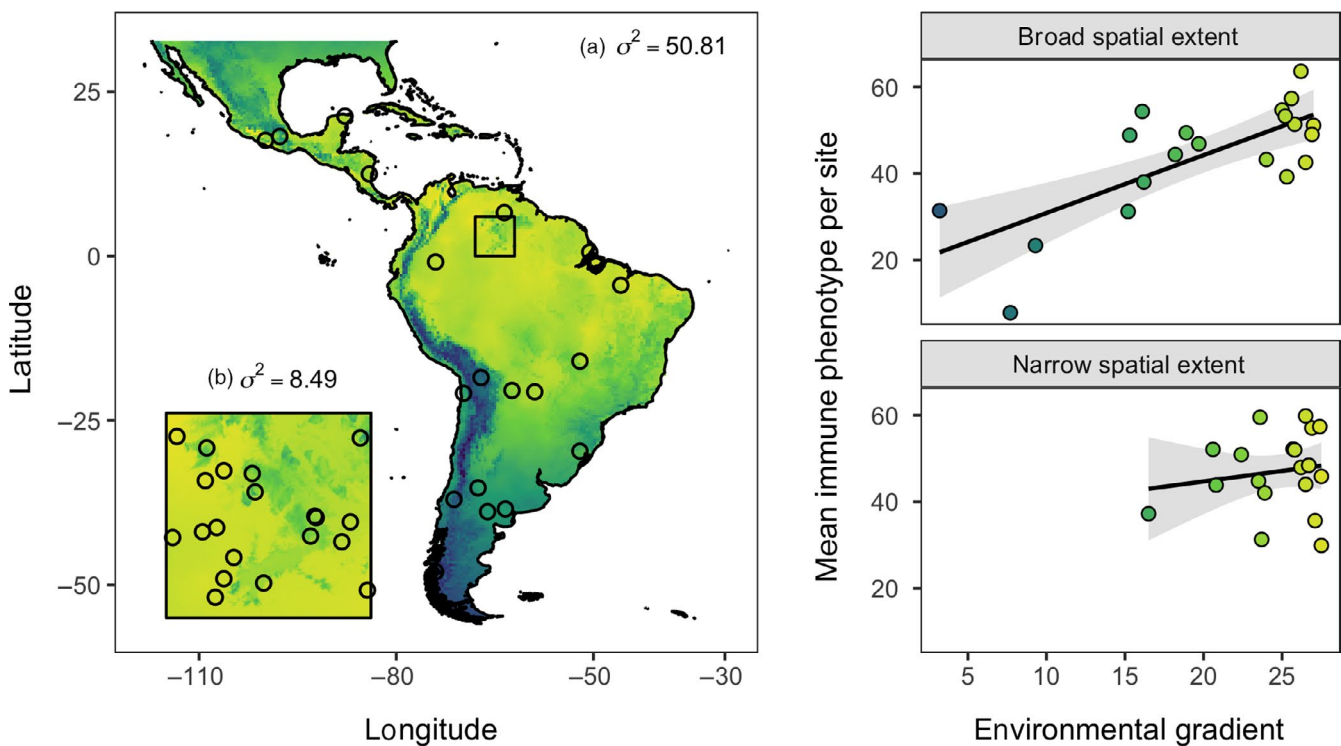
density). Likewise, many large-scale sources of environmental variation, such as urbanization, agricultural change, geographic range limits and latitudinal gradients, defy categorization into a few testable treatments. In other cases, field experiments may be logistically challenging or pose ethical concerns (e.g. manipulating

the degree of habitat fragmentation). Given these potential limitations, comparisons of immunity between many replicate wild populations across a sufficiently broad spatial extent can help to quantify environmental variation needed for macroecology and, in turn, determine the importance of environmental factors across multiple scales (Wiens, 1989; Figure 1). In an iterative fashion, such work could facilitate developing hypotheses for field experiments and captive studies that can triangulate on causal inference (Plowright, Sokolow, Gorman, Daszak, & Foley, 2008).

In this review, we introduce how such large-scale approaches to ecoimmunology could elucidate the spatial determinants of infection. Macroecology, the study of large-scale patterns in animal abundance, diversity and distributions (Gaston & Blackburn, 2008), has identified many broad-scale determinants of infectious disease (Stephens et al., 2016), including latitudinal gradients in parasite species richness and differentiating the various environmental drivers of emerging infections (Brierley, Vonhof, Olival, Daszak, & Jones, 2016; Dallas et al., 2018; Dunn, Davies, Harris, & Gavin, 2010). Similar approaches (i.e. macroimmunology) could facilitate novel insights into fundamental questions of how environmental variation alters immunity. Do immune profiles follow biogeographic patterns? How do range expansions affect host defence? Does urbanization have consistent impacts on immune

function? Delineating spatial patterns in immunity and their underlying environmental mechanisms could improve predictions about where wild individuals may be vulnerable to infection or act as sources of emerging parasites. Moreover, understanding the macroecological basis of host traits such as resistance (i.e. the ability to inhibit or reduce infection) or competence (i.e. the ability to transmit new infections to susceptible hosts or vectors) could be particularly informative, as these traits provide mechanistic links between within- and between-host infection processes (Martin, Burgan, Adelman, & Gervasi, 2016; Roy & Kirchner, 2000) and may be less prone to the sampling biases found in global parasite datasets (Han, Kramer, & Drake, 2016).

We here aim to generate a research agenda for macroimmunology akin to that developed for the macroecology of infectious disease (Morand, Bordes, Pisanu, Bellocq, & Krasnov, 2010; Stephens et al., 2016). We first provide an overview of the key habitat factors that are likely to generate most spatial variation in immunity (Table 1). We next perform a systematic review of the ecoimmunology literature to assess the frequency of spatial approaches and to characterize research efforts to date according to host taxa, study design and statistical methods. By critically appraising these studies, we use our findings to motivate a discussion of geostatistical and spatial modelling tools that can improve inference about associations between



**FIGURE 1** Conceptual schematic for how sampling designs over broad spatial extents (a) capture more variance ( $\sigma^2$ ) in environmental conditions than over narrow spatial extents (b) and how inference for spatial relationships with immunity is affected by scale. The map displays environmental conditions (e.g. annual mean temperature for illustrative purposes) at the resolution of 2.5 minutes latitude from WorldClim (Hijmans, Cameron, Parra, Jones, & Jarvis, 2005). Data were extracted from 20 randomly distributed sampling points using the RASTER package in R within a large and a narrow spatial extent. Estimates of  $\sigma^2$  in the underlying environmental gradient are shown for both sampling designs. Mean immune phenotype data per site were generated by adding normally distributed noise to the environmental gradient; lines show fits from generalized least square models accounting for the spatial dependence of sampled sites. The sampling design using a broad spatial extent reveals a strong association between environmental variation and immunity ( $\chi^2 = 20.5$ ), whereas that using a narrow spatial extent detects no relationship ( $\chi^2 = 0.5$ )

the environment and immunity while also guiding sampling designs for future large-scale studies. Given the early nature of macroimmunology, we outline research questions that are especially well poised to answer through spatial methods. We provide methodological recommendations for addressing such questions, including integrating smaller-scale study designs to facilitate causal inference, and we outline macroecological approaches for conducting the broad data syntheses required to identify generalizable patterns.

## 2 | SPATIAL FACTORS DRIVING IMMUNE VARIATION

### 2.1 | Parasite pressure

Differential exposure to parasites across a landscape, as well as spatial variation in highly virulent parasite genotypes, can shape immunity through short-term plastic changes as well as selection. For example, regions with greater parasite diversity or active transmission can induce plastic changes in antibody concentrations (Karsten & Rice, 2006), while infection hotspots over long timescales or invasions of virulent parasites can select for frequency changes in protective immune genes and thus the evolution of resistance (Bonneaud, Balenger, Zhang, Edwards, & Hill, 2012; Tschirren, 2015; Table 1). Major histocompatibility complex (MHC) diversity also often correlates with spatial variation in parasites (Savage & Zamudio, 2016), signalling parasite-mediated selection.

Spatial links between parasite pressure and host immunity can occur across localized and broad scales driven by environmental gradients. For example, small-scale variation in the distance to poultry farms, a predictor of avian malaria risk in Berthelot's pipits *Anthus berthelotii*, explained variation in MHC allele frequencies (Gonzalez-Quevedo, Davies, Phillips, Spurgin, & Richardson, 2016). At larger scales, latitudinal gradients in immunity have been observed across taxa ranging from insects (Meister, Tammaru, Sandre, & Freitak, 2017) to birds and bats (Becker, Nachtmann, et al., 2019; Hasselquist, 2007) and could reflect latitudinal gradients in parasite species richness (Lindenfors et al., 2007).

### 2.2 | Abiotic and biotic factors

Given a finite amount of energetic and nutritional resources, the principle of allocation suggests that individuals must trade-off between immunity and other costly traits such as reproduction (Lochmiller & Deerenberg, 2000). Spatial heterogeneity in abiotic and biotic conditions may shape such trade-offs and accordingly alter spatial patterning of immune phenotypes. For example, spatial variation in water conductivity explained variation in innate immunity of *Gammarus pulex* (Cornet, Biard, & Moret, 2009; Table 1). Variation in abiotic conditions can also modify energetic trade-offs at large spatial scales; for example, tree swallows *Tachycineta bicolor* at the northern limits of their geographic range showed more dramatic trade-offs among multiple

arms of immunity and with reproduction than birds at their southern range limit (Ardia, 2005, 2007).

Biotic conditions can also impact host energetics and immune investment. As food is limiting for many wildlife, resource availability is a key driver of defence (Strandin, Babayan, & Forbes, 2018). Whereas the allocation model predicts negative trade-offs between immunity and costly traits, the acquisition model can explain positive correlations: if hosts can acquire more resources, energy can be allocated to both immunity and other costly traits (Van Noordwijk & de Jong, 1986). In turn, habitats with more food should allow individuals to invest more in immunity and traits such as reproduction (Brzęk & Konarzewski, 2007). Population density can further shape spatial patterns in immunity. High population densities could suppress immunity from overcrowding (Becker, Cziráj, Volokhov, et al., 2018; Table 1). However, high population density could instead increase parasite pressure and select for greater investment in immunity; for example, bird T-cell-mediated responses were highest in very dense host populations (Møller, Martín-Vivaldi, Merino, & Soler, 2006).

### 2.3 | Anthropogenic factors

Expanding human populations are changing environments across spatial scales from habitat fragmentation, urbanization and agriculture (Acevedo-Whitehouse & Duffus, 2009). Anthropogenic factors can shape spatial patterns in immunity by altering the above two processes (i.e. changing parasite pressure and abiotic or biotic conditions) and by exposing individuals to novel stressors such as contaminants (Martin et al., 2010).

Anthropogenic factors can alter parasite pressure as well as abiotic and biotic conditions, thereby indirectly shaping immunity. For example, tree swallows *Tachycineta bicolor* in more agricultural habitats had stronger bacterial killing ability (BKA) than birds in less agricultural habitats, potentially owing to elevated parasitism (Schmitt, Garant, Bélisle, & Pelletier, 2017; Table 1). Vampire bats *Desmodus rotundus* in more agricultural habitats also had stronger BKA, instead likely signalling improved defence from more food through abundant livestock prey (Becker, Cziráj, Volokhov, et al., 2018; Table 1). Given that these similar patterns can stem from distinct environmental mechanisms, data-driven syntheses to assess how anthropogenic habitats influence immunity across spatial scales are especially needed (Messina, Edwards, Eens, & Costantini, 2018).

Contaminants can directly shape defence by altering the synthesis or function of immune parameters and by disrupting parts of the neuroendocrine system that control immune development and growth (Desforges et al., 2016). Hosts are exposed to spatial variation in contaminants by proximity to point (e.g. refineries) and nonpoint (e.g. agricultural runoff) sources, in turn generating spatial variation in immunity. For example, tree swallows breeding in mercury-contaminated habitats exhibited weaker immune responses to phytohaemagglutinin challenge than birds in reference habitats



(Hawley, Hallinger, & Cristol, 2009), and Algerian mice *Mus spretus* sampled from a polluted site showed distinct immune gene expression relative to mice from uncontaminated habitats (Ruiz-Laguna, Vélez, Pueyo, & Abril, 2016).

### 3 | CRITICAL APPRAISAL OF MACROIMMUNOLOGY

Given that various spatial factors can affect immunity, spatially focused studies can help to differentiate distinct environmental mechanisms underlying such geographic patterns. Although these studies can be logistically challenging, growing macroecological efforts suggest many spatial processes can be distinguished. For example, proxies of water quality were associated with spatial variation in sea fan coral *Gorgonia ventalina* innate immunity, whereas historical disease prevalence had no impact, suggesting a more dominant role of current abiotic conditions in shaping host defence (Couch, Mydlarz, Harvell, & Douglas, 2008; Table 1). To assess the degree to which macroimmunology studies can provide such inferences, we conducted a systematic review to (a) quantify how common spatial studies are in ecoimmunology, (b) how often such studies test the effects of these hypothesized spatial factors and (c) describe spatial studies according to host taxa, spatial replication and extent, immune measures and the use of spatial statistical methods.

#### 3.1 | Literature review

We conducted systematic searches in Web of Science, PubMed and CAB Abstracts in October 2018 using the following string: (wild\*) AND ('immune defence' OR 'immune response' OR 'immune function' OR 'immune phenotype' OR 'immune profiles' OR 'immunity' OR ecoimmunology) AND (environment\* OR geograph\* OR latitud\* OR landscape\* OR habitat\* OR 'populations' OR range\* OR biotic\* OR abiotic\* OR anthropogo\*) NOT (human\* OR domestic\* OR captiv\* OR experiment\* OR plant\* OR aquacultur\*). These produced 3,657 studies after excluding duplicates (Figure S1). We followed a systematic protocol to screen titles, abstracts and full texts to include studies of immunology in wild systems. From the remaining 456 studies, we recorded the wildlife taxon and whether studies sampled more than one site. This sample likely represents only a subset of ecoimmunology, and we interpret results accordingly.

For studies that sampled more than one site, we recorded (a) host species, (b) number of sites, (c) scale of analysis, (d) immune measures, (e) whether studies assessed spatial autocorrelation and (f) spatial variation in immunity, (g) statistical methods, (h) whether studies quantified spatial variation in environmental conditions and related this to immunity, (i) individual covariates included in the spatial analysis, (j) if the study also assessed seasonality and (k) spatial extent. Most studies did not report extent, which we

estimated using the longitude and latitude of the most distant sites with the GEOSPHERE package in R (Hijmans, Williams, Vennes, & Hijmans, 2017).

#### 3.2 | Statistical approach

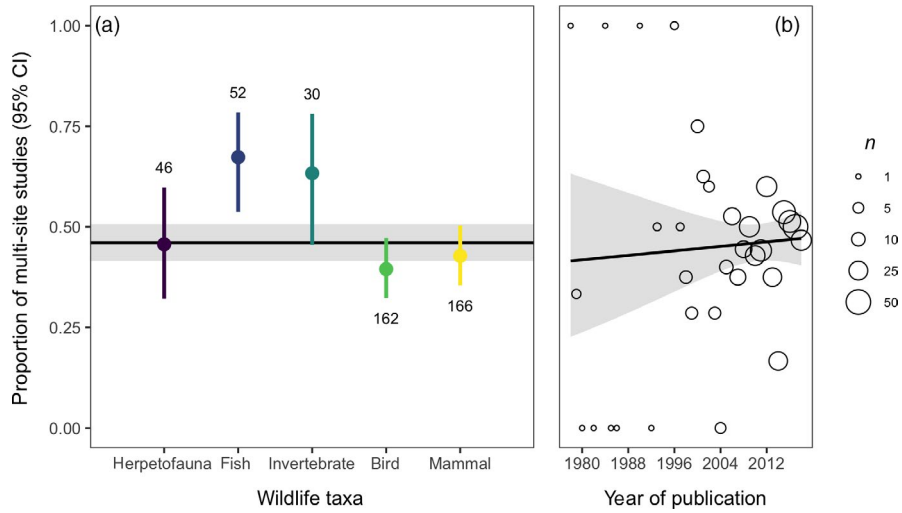
We used the PREVALENCE package to estimate the prevalence of multi-site studies. To test whether prevalence varied across taxa, we fit a generalized linear model (GLM) with binomial errors and a logit link. To test how the proportion of multi-site studies has fluctuated over time, we fit a generalized additive model (GAM) with year as a smoothed term using the MGCV package (Wood, 2006).

In our dataset of only multi-site studies, we performed descriptive analyses to describe the diversity of immune measures, how often studies assessed spatial variation and what spatial factors were tested. We classified immune measures into seven categories: antigen challenge (e.g. in vivo and in vitro), functional defence (e.g. microbial killing assays), immune cells (e.g. leukocyte counts), immune genes (e.g. individual expression, MHC), immune organs (e.g. spleen mass, bursa of Fabricius), immune proteins (e.g. acute phase, immunoglobulins) and other (e.g. reactive oxygen species). We also assessed whether studies measured innate or adaptive immunity and used  $\chi^2$  tests to assess whether measures were distributed differentially across taxa. We also estimated the proportion of multi-site studies that assessed spatial variation in immunity, using another  $\chi^2$  test to quantify how these spatial factors varied across taxa.

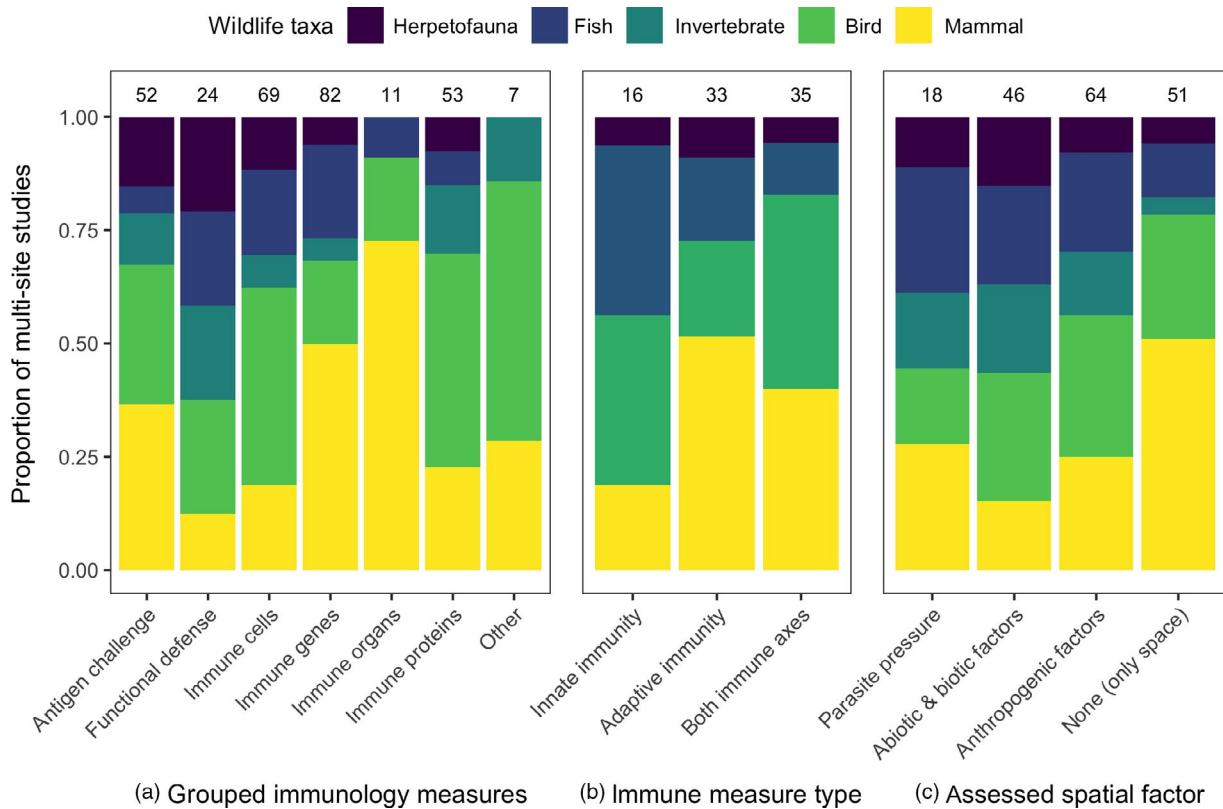
We next restricted analyses to studies reporting the number of sites sampled. We used the FITDISTR package to fit four distributions to the number of sites per study to assess skew in spatial sampling efforts (Delignette-Muller & Dutang, 2014). We used Akaike information criterion (AIC) to select the appropriate error distribution to next use in a GLM testing how spatial replication varied with taxa (Burnham & Anderson, 2002). We lastly tested whether spatial replication scaled positively with spatial extent, which would suggest that sampling efforts match study scale (Wiens, 1989). We  $\log_{10}$ -transformed spatial extent as our response, included the number of sites as the predictor, and compared three models: a linear model, a linear model with a quadratic term and a linear model with log-transformed number of sites (i.e. a log-log model).

#### 3.3 | Emerging methodological patterns

Of the 456 ecoimmunology studies from our literature sample, 210 assessed immune variation across multiple sites (46%, 95% CI: 42%–51%). This proportion varied by taxa ( $\chi^2 = 16.70$ ,  $p < .01$ ), with fish having more multi-site studies (67%) than birds (40%;  $z = 3.41$ ,  $p < .01$ ) or mammals (43%;  $z = 3.03$ ,  $p = .01$ ; Figure 2a). The proportion of multi-site studies showed no annual change ( $\chi^2 = 0.17$ ,  $p = .68$ ; Figure 2b). Therefore, although spatial approaches have been fairly common within ecoimmunology, their use has varied across taxa and been constant over time.



**FIGURE 2** The proportion of our sample of ecoimmunology studies ( $n = 456$ ) that studied multiple host populations. (a) The estimated prevalence across all data is shown in black with the 95% confidence interval in grey (46%); stratification of these data by wildlife taxa suggested that fish had a higher proportion of multi-site studies than birds and mammals, although the latter two taxa had been studied more frequently. (b) While the overall number of multi-site studies has increased for ecoimmunology over time (points are scaled by the number of studies per year), the relative abundance of multi-site studies has remained unchanged since the 1980s



**FIGURE 3** Description of immunology data and spatial mechanisms assessed in our sample of multi-site studies in the ecoimmunology literature. For all 210 studies included in our systematic review, we classified immunology data into seven categories (a). Where possible, we also assessed if studies measured innate or adaptive immunity (b). For the 70% of studies that assessed spatial variation in wildlife immunology, we classified if studies assessed each of the three mechanisms linking environmental and immunological variation as well as space only (c). Barplots are stacked by wildlife taxa

The most common immune measures were immune genes, immune cells, antigen challenge and immune proteins; 32% of studies used assays from multiple categories (67/210). Assays that describe

functional (parasite-specific) defence (e.g. microbicidal ability, resistance to parasite challenge) were rare (11%). Immune metrics and taxon were associated ( $\chi^2 = 60, p < .001$ ; Figure 3a); mammal studies

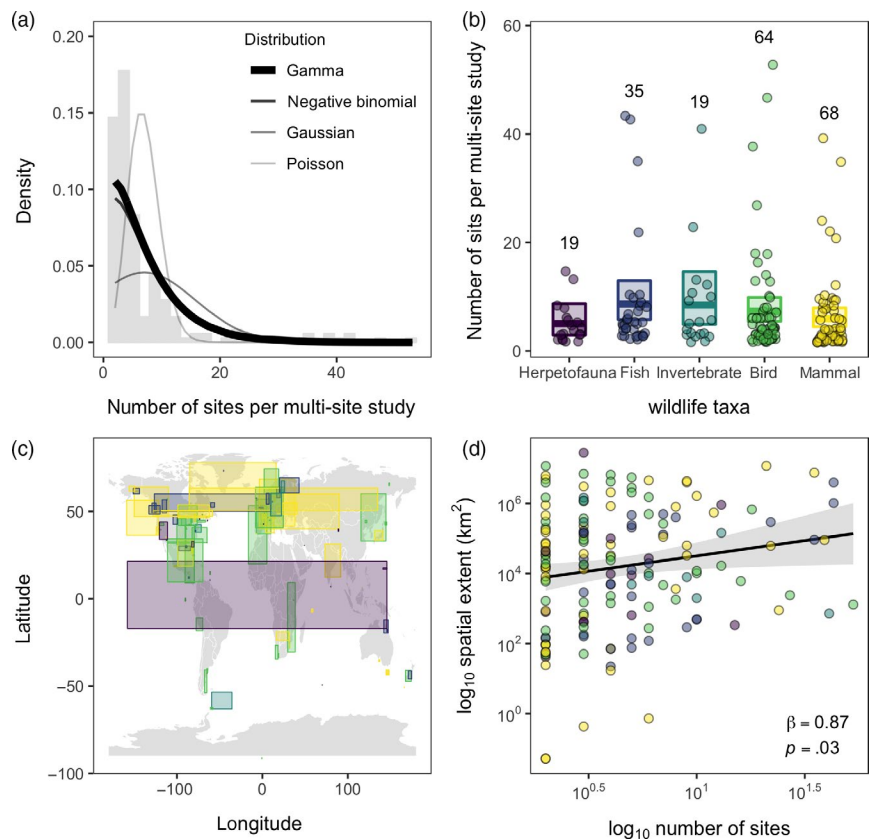
were more likely to assay immune genes and organs, bird studies were more likely to assay immune cells and proteins, bird and mammal studies were more likely to use antigen challenge, and the rare assays that describe functional defence were evenly distributed (Figure 3a). Of the 84 studies for which measures could be classified into innate or adaptive immunity (excluding invertebrates), most studies quantified adaptive immunity (39%) or both measures (42%); this pattern did not vary across taxa ( $\chi^2 = 9.59$ ,  $p = .15$ ; Figure 3b).

Many multi-site studies (168/210) also explicitly assessed spatial variation in immunity. Most of these 168 studies tested this variation with at least one spatial factor (70%), whereas the remainder included site as a fixed effect or used a purely spatial covariate (e.g. latitude, island vs. mainland). Few studies (11%) tested parasite pressure using spatial measures such as infection prevalence, parasite richness and population exposure history. Approximately one-quarter of studies (27%) tested abiotic or biotic conditions through spatial measures such as altitude, colony size or temperature. More studies (38%) tested anthropogenic factors, using spatial measures such as contaminant exposure, intensity of urbanization or habitat fragmentation. Only 10 studies assessed multiple spatial factors simultaneously. The proportion of studies that tested spatial factors varied by taxa ( $\chi^2 = 22.48$ ,  $p = .03$ ), with 50% of each spatial factor comprising studies of mammals and birds (Figure 3c). Thus, whereas multi-site studies often examined spatial patterns in immunity and tested environmental predictors of this variation, rarely did they test multiple spatial hypotheses. To assess whether this could be an issue of statistical power, we next quantified spatial replication and tested whether this matched spatial extent.

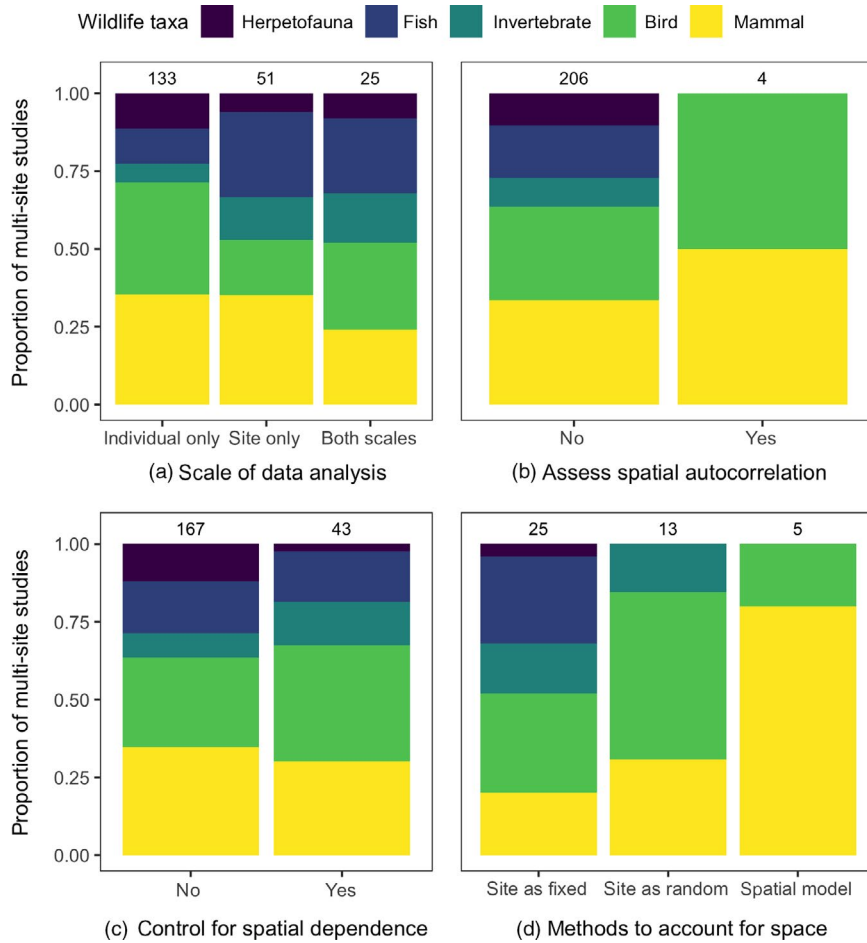
The degree of spatial replication was best described using a Gamma distribution ( $w_i = 1.00$ ; Table S1) with a long right tail and a median of four sites (Figure 4a). A GLM with Gamma-distributed errors showed that spatial replication did not vary across taxa ( $\chi^2 = 4.12$ ,  $p = .39$ ; Figure 4b). We tested whether spatial extent scaled positively with the spatial extents of our studies (Figure 4c). For the 157 studies where extent was reported or could be derived, a log-log model was supported over a linear term for spatial replication ( $w_i = 0.56$ ), whereas a quadratic term was only marginally supported ( $\Delta AIC = 1.79$ ; Table S2). The log-log model showed that spatial extent was positively associated with spatial replication ( $F_{1,155} = 4.95$ ,  $p = .03$ ), denoting a power law relationship. The slope was less than one ( $\beta = 0.87$ ), suggesting that the effect of spatial replication on spatial extent weakens at large scales (Figure 4d). This pattern was replicated by the quadratic linear model (Figure S2). This result implies that studies with few sites match their spatial extent. However, studies with larger extents did not display a similar increase in spatial replication, suggesting limited ability to infer how environment shapes immunity (e.g. Figure 1).

Most macroimmunology studies assessed data at the individual scale (64%), with fewer studies operating at the scale of sites (e.g. aggregating individual data; 24%) or using both scales (12%). These scales were differentially distributed across taxa ( $\chi^2 = 16.74$ ,  $p = .03$ ), with mammal and bird studies more often assessing individual variation (Figure 5a). Only four studies assessed spatial autocorrelation (Figure 5b; all with Mantel tests of isolation by distance). Only 20% of studies controlled for pseudoreplication by site (43/210); this was consistent across taxa ( $\chi^2 = 5.63$ ,  $p = .24$ ; Figure 5c). Most of these 43 studies (58%) included site as a fixed effect. Only 30% used site

**FIGURE 4** Spatial replication and spatial extent in multi-site ecoimmunology studies. (a) The histogram for the number of sites per study (e.g. spatial replication) is shown in grey with the fitted distributions (size and shading are proportional to the Akaike weights; Table S1). (b) The means and 95% confidence intervals from a generalized linear model with Gamma-distributed errors are shown for wildlife taxa alongside the raw data; spatial replication did not vary across wildlife. (c) Estimated spatial extent is shown for all 157 studies in which coordinate data were available or for which extent was reported, with shading of the bounding boxes corresponding to wildlife taxa. (d) Fitted values and 95% confidence intervals (grey) for the top linear model describing the relationship between spatial replication and spatial extent (both with a  $\log_{10}$  transformation)







**FIGURE 5** Statistical approaches used in our sample of multi-site studies within the ecoimmunology literature. For all 210 studies included in our systematic review, we quantified the scale of data analysis (a), if studies assessed spatial autocorrelation (b) and if studies controlled for spatial dependence (c). For the 43 studies that controlled for spatial dependence, we also quantified how space was treated in the analyses. Barplots are stacked by taxa

as a random effect in a mixed model (GLMM; 13/43), and only 12% used spatial statistical models. These statistical methods did not vary across taxa ( $\chi^2 = 13.06$ ,  $p = .12$ ; Figure 5d).

#### 4 | SPATIAL STATISTICAL METHODS FOR ECOIMMUNOLOGY

In addition to detecting generally low spatial replication in macroimmunology, these descriptive analyses highlight the rarity of quantifying spatial autocorrelation and controlling for spatial dependence. We here describe tools from geostatistics and spatial analysis to assess and control for spatial variation and to guide future spatial sampling designs. Because the application of statistical methods to infectious disease data has been reviewed elsewhere (e.g. Pullan, Sturrock, Magalhaes, Clements, & Brooker, 2012), we highlight concepts and tools more specific to ecoimmunology than to epidemiology.

Ecoimmunology data are mostly continuous sources of spatial variation at the individual scale rather than at discrete spatial units; binary data (e.g. resistant genotypes) are also possible. Prior to hypothesis tests of how environmental variation shapes immunity, quantifying continuous spatial dependence can provide

important insights about the spatial scale at which such effects occur (Diniz-Filho, Bini, & Hawkins, 2003). While immunity can be compared between discrete sites or populations, spatial dependence can be characterized with global and local measures of autocorrelation. Global Moran's  $I$  varies from  $-1$  to  $1$ , from perfectly dispersed to perfectly clustered spatial data (Moran, 1950). Spatial correlograms can further help estimate local autocorrelation as a function of inter-site distance (Koenig & Knops, 1998). The shape of the correlogram can provide insight into the environmental processes generating the spatial pattern (Legendre & Fortin, 1989). Correlograms often show a linear or exponential decline with increasing distance, suggesting a highly localized spatial mechanism. Recent work on red deer *Cervus elaphus* illustrates such fine-scale autocorrelation and suggests that environmental processes can shape defence within even an individual's home range (Albery, Becker, Kenyon, Nussey, & Pemberton, 2018). In contrast, correlograms applied to vampire bat leukocytes demonstrated autocorrelation at broad scales (thousands of kilometres), suggesting that conditions of the latitudinal range margins were more important determinants of immunity than local predictors (Becker, Nachtmann, et al., 2019). Whereas our sample had no analyses that used correlograms, studies did use Mantel tests to quantify if similarity in immunity between sites is predicted by inter-site distance (Figure 5b). Semi-variograms can also provide

more precise estimates of spatial dependence (Goovaerts, 1997). Semi-variance (the dissimilarity between observations) increases with distance until a maximum value is obtained (i.e. the sill); the corresponding inter-site distance is the estimated 'range' of spatial dependence, which can indicate the spatial scale of environmental drivers.

Quantifying spatial dependence can also assist with sampling designs, which often involve trade-offs between spatial and temporal replication (Plowright, Becker, McCallum, & Manlove, 2019). Researchers may first decide to intensively sample over space but at a fixed time. As seasonality could also shape immunity while having different effects across space, sampling at a small number of uniform timepoints across populations (e.g. winter, summer) may be particularly informative; only 13% of multi-site studies assessed seasonality (this did not vary with taxa;  $\chi^2 = 0.66, p = .95$ ), highlighting an important area for future work. Quantifying spatial dependence from pilot data or from similar systems could identify the spatial scales at which sampling should occur to obtain sufficient immunological variance. For example, strong autocorrelation at small scales suggests sites could be relatively close, whereas a large range estimate suggests sites could be further apart to be subjected to sufficient spatial variation. Knowing the scale of spatial dependence can also facilitate how to best spatially subdivide a given sampling grid for random stratified designs, which can limit spatial site clusters generated by purely random sampling (Smith, Anderson, & Pawley, 2017).

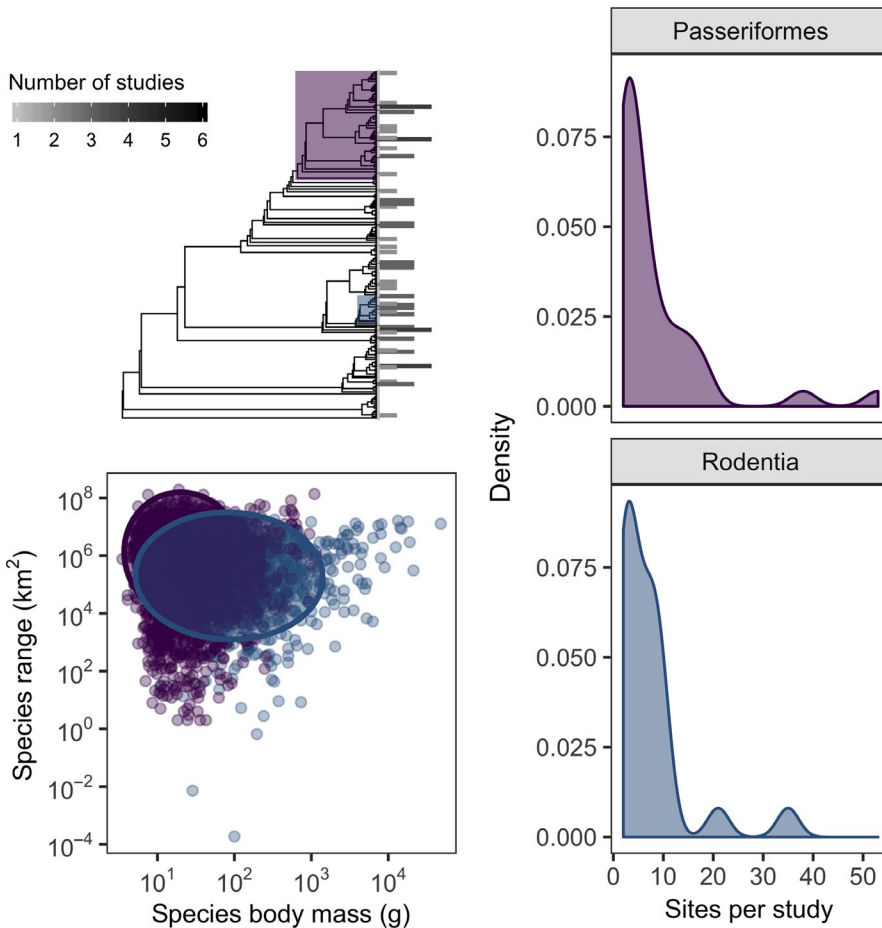
Our review also suggests macroimmunology studies should better control for spatial dependence. Ignoring spatial dependence in statistical analyses can inflate model coefficients, underestimate standard errors and bias inference (Legendre, 1993). Approximately a quarter of studies (24%) used site-aggregated data; although this could facilitate accounting for space with traditional generalized least squares models, aggregating individual immunity data can obscure intra- and inter-population variation (Downs & Dochtermann, 2014). Aggregating data further limits the ability to account for individual-level covariates, such as reproduction and age, that can moderate relationships between spatial predictors and immunity (Merrill, Stewart Merrill, Barger, & Benson, 2019). Common individual-level covariates in our multi-site studies included morphology (e.g. mass), sex and age (Figure S3). We strongly encourage greater use of GLMMs that include site as a random effect to allow the partitioning of immunological variance into repeatability within and between sites as well as quantifying the importance of both individual- and habitat-level factors. Furthermore, GLMMs can accommodate spatial correlation structures to account for the spatial distribution of sites (Zuur, Ieno, Walker, Saveliev, & Smith, 2009), and autocorrelation measures can be derived to ensure no residual spatial dependence. Similarly, GAMs can account for nonlinearity in environmental predictors while including a smoothed interaction of longitude and latitude or a spatial correlation structure (Wood, 2006). Integrated Nested Laplace Approximation (INLA) is also becoming popular owing to its computational efficiency and flexible model construction (Blangiardo, Cameletti, Baio, & Rue, 2013). INLA incorporates a two-dimensional spatial random effect that can be plotted to investigate hot- and cold spots of immunity. One INLA case study

highlighted spatial agreement and discordance between several immune metrics and parasitism in red deer (Albery et al., 2018). Greater adoption of spatial statistics will strengthen our understanding of how the environment shapes immune defence while minimizing potential statistical artefacts.

## 5 | FUTURE DIRECTIONS FOR MACROIMMUNOLOGY

Our synthesis illustrates the growing interest in macroimmunology and assessing spatial variation in wildlife defence. However, our results also suggest the field is in its early stages with much room to expand. Although spatial approaches to ecoimmunology are common, spatial replication is low overall, especially for large-scale studies. This limits the ability of such studies to capture the broad environmental variation required for macroecology (Wiens, 1989), and underpowered analyses linking spatial covariates with immunity may risk false negatives (e.g. Figure 1). Most studies do not control for spatial dependence, which can risk false positives (e.g. underestimating standard errors). Moreover, not characterizing spatial dependence is a missed opportunity to develop data-driven hypotheses and sampling designs. More generally, whereas ecoimmunology research on species-level heterogeneity has begun to integrate across studies (e.g. Brace et al., 2017; Downs, Schoenle, Han, Harrison, & Martin, 2019), work on environmental heterogeneity has largely remained idiosyncratic (however, see Morand et al., 2010 and Messina et al., 2018).

To direct future studies in macroimmunology, we lastly outline research questions that are especially well poised to answer through spatial approaches, provide methodological recommendations for addressing such questions and outline macroecological approaches for conducting the broad data syntheses required to assess generalizable patterns. Given the broad taxonomic representation of studies included in our synthesis, we focus this primarily on birds and mammals. These taxa had greater numbers of multi-site studies, were especially well-studied for anthropogenic change and their studies were more likely to assess spatial variation in immunity and control for spatial dependence. In particular, we draw from work on passerines and rodents, which have several advantageous characteristics (Figure 6). Their small body sizes mean that many species are easy to live capture, their small home ranges allow many site replicates and their broad geographic ranges facilitate obtaining high environmental variation (Hasselquist, 2007; Lindstedt, Miller, & Buskirk, 1986). Immunological resources from domestic birds and laboratory rodents can also facilitate comparative work, although translating these reagents to wild species is not without its challenges (Martinez, Tomás, Merino, Arriero, & Moreno, 2003; Pedersen & Babayan, 2011). Many passerines and rodents are common in anthropogenic habitats and are reservoirs for zoonotic and economically important parasites, which is relevant for linking environmental change, immunity and spillover (Han et al., 2016;



**FIGURE 6** Passerines and rodents are two possible model taxa for macroimmunology. The phylogeny of the 270 species included in our literature sample is displayed with the number of studies per species shown as bars (colour is proportional to size); highlighted are the clades containing these two orders. We visualize how these orders overlay in trait space (body size and geographic range size) to emphasize the relative ease of live capture and sampling these species alongside their broad distributions (encompassing high environmental variation). Also displayed are the distributions of spatial replication per study for both orders. See the Online Supplement for more information about sources of phylogenetic and trait data

Reed, Meece, Henkel, & Shukla, 2003). Studies of passerines and rodents generally had spatial replication above the study-level median (Figure 6), with species such as the tree swallow, great tit *Parus major*, house finch *Haemorhous mexicanus*, house sparrow *Passer domesticus*, house mouse *Mus musculus*, bank vole *Myodes glareolus* and field vole *Microtus agrestis* being especially well represented in our sample (Table S3).

## 5.1 | Priority areas for future research

As highlighted in our critical appraisal, most studies that assessed spatial variation in immunity did so through anthropogenic or purely spatial gradients. Within these factors, we focus on three priority questions posed early in this review: does immunity follow biogeographic patterns, how do range expansions affect defence and does urbanization have consistent impacts on immune phenotypes? Such topics are united in dealing with large spatial scales and integrating several environmental factors. We here summarize insights from past studies and highlight predictions to test with spatial sampling of well-studied species (Table S3) and macroecological data synthesis.

Latitudinal studies of immunity have held particular appeal for ecoimmunology, offering potential for simple laws in patterns of host resistance (Hasselquist, 2007; Morand et al., 2010).

Approaches have ranged from studying closely related species pairs across latitudes (Møller, 1998) to field studies of several temperate and tropical populations (Adelman, Córdoba-Córdoba, Spoelstra, Wikelski, & Hau, 2010; Ardia, 2005; Martin, Hasselquist, & Wikelski, 2006; Owen-Ashley, Hasselquist, Råberg, & Wingfield, 2008). These patterns have been well studied in passerines, for which birds closer to the equator tend to show stronger humoral but not cell-mediated immunity (Hasselquist, 2007). Rodents have been relatively understudied, with latitude being a less consistent predictor of defence (Morand et al., 2010; Pyter, Weil, & Nelson, 2005). An outstanding hypothesis is whether such latitudinal gradients reflect latitudinal gradients in parasitism. Although past work has found distinct immune phenotypes between temperate and tropical populations, such differences can stem from spatial gradients not only in parasitism but also in breeding phenology, life history or abiotic conditions. For example, vampire bats from their latitudinal range limits had high ratios of heterophils to lymphocytes, in contrast to the prediction that these would indicate elevated inflammation close to the equator due to higher parasite risks (Becker, Nachtmann, et al., 2019). In many systems, latitudinal variation in parasitism remains to be tested (Hasselquist, 2007; Morand et al., 2010), while other studies find infection to be higher at range limits (e.g. Briers, 2003) or demonstrate inconsistent patterns with latitude that may reflect transmission mode (Clark,

2018; Dallas et al., 2018; Lindenfors et al., 2007). More extensive spatial sampling efforts alongside assessment of parasite pressure could help differentiate the importance of parasite gradients from other environmental factors.

Range expansions and biological invasions are another priority for macroimmunology. Immunity can not only facilitate the success of species introductions but also determine whether invasive individuals are more likely to serve as reservoir hosts for novel (i.e. spillover) or native (i.e. spillback) parasites (Kelly, Paterson, Townsend, Poulin, & Tompkins, 2009; Lee & Klasing, 2004). Various hypotheses have been proposed for drivers of variation in immunity across an invasion, including that introduced hosts may exhibit damped inflammatory responses given high energetic costs of this defence and greater investment in reproduction, that hosts in more recently established populations should instead invest more in humoral immunity given possibly elevated parasite risks, and that founder events during expansions could lead to reduced genetic diversity and weaker defence (Lee & Klasing, 2004; Travis et al., 2007). Such hypotheses can be most readily assessed through comparing immunity across a gradient of recently established and native range populations. Work on passerines and rodents has facilitated several tests of these ideas. Invasive house mice and black rats *Rattus rattus* in Senegal display stronger natural antibody responses and higher inflammatory responses compared to those in more established populations, suggesting that greater parasite exposure at the invasion front drives immunity (Diagne et al., 2017). Similarly, inflammation has likely mitigated invasion success of house sparrows in Kenya; the expression of toll-like receptors (TLRs) 2 and 4 is higher in range-edge birds than birds closer to the site of introduction (Martin, Coon, Liebl, & Schrey, 2014; Martin, Liebl, & Kilvitis, 2015). Whether such patterns arise from protective effects of TLR expression, the propensity of high TLR expression to mitigate the costs of immunity, or a balance of both processes remains an area of active investigation (Martin et al., 2017). Spatial sampling across more geographic and taxonomically diverse systems where range expansions occur will facilitate assessing any general associations between invasions and immune defence.

Lastly, urban–rural gradients offer several opportunities for macroimmunology. Although many aspects of urbanization can shape immunity (French, Webb, Hudson, & Virgin, 2018; Ouyang et al., 2018), the availability of anthropogenic resources has received increasing attention (Altizer et al., 2018; Becker, Streicker, & Altizer, 2015). Spatial studies of passerines suggest that urban (and suburban) habitats with supplemental food are associated with lower ratios of heterophils to lymphocytes and greater microbicidal ability (Wilcoxon et al., 2015). Similarly, anthropogenic food may more broadly increase both innate and adaptive defences (Strandin et al., 2018). Such patterns are consistent with predictions from the acquisition model, where access to more resources can result in allocating energy to immune functions with differing costs (Van Noordwijk & de Jong, 1986), which may likewise explain patterns of general upregulation of immune response in urban great tits and

other passerine species (Fokidis, Greiner, & Deviche, 2008; Watson, Videvall, Andersson, & Isaksson, 2017). The acquisition model may also explain how urbanized species can obtain high population densities alongside such immunological differences, if urbanized hosts can invest more in both defence and reproduction (Oro, Genovart, Tavecchia, Fowler, & Martínez-Abraín, 2013). Spatial studies of urbanization can also test how defence differs between island and mainland populations. Passerine studies have tested the prediction that islands have lower parasite pressure that, in turn, lowers immune investment (Lindström, Foufopoulos, Pärn, & Wikelski, 2004), although comparative and case studies have found weak or opposite patterns (Matson, 2006; Matson, Mauck, Lynn, & Irene, 2013). As urbanization can reduce connectivity (Munshi-South & Kharchenko, 2010), urban–rural sampling gradients could provide additional assessments. On ecological timescales, isolated populations may lose herd immunity and be more vulnerable to pathogens, as suggested for Australian flying foxes (*Pteropus* spp.; Plowright et al., 2011). Bats in particular pose several challenges for spatial studies of immunity when compared to passerines and rodents (e.g. lack of reagents, large home ranges). However, the potential insights about parasite spillover to humans and domestic animals may be especially important from an applied standpoint, when considering that bats host many zoonoses and are increasingly affected by urbanization (Kessler et al., 2018).

## 5.2 | Methodological recommendations

To facilitate testing such questions and improve inference in macroimmunology, we highlight several methodological recommendations for large-scale field studies. These build upon the various benefits gained from exploratory geostatistical tools and spatial statistical methods.

Although we recommend using geostatistical tools such as correlograms to identify the range of spatial dependence and guide sampling decisions (e.g. aid in decisions for the distance between field sites), sufficient data may not exist for a given host system or for closely related species. Researchers could instead use semi-random site distributions (Abolins et al., 2018) or spatial gradients, such as sampling latitudinally (Adelman et al., 2010), at the core and limits of a geographic range (Ardia, 2007), or along range expansions of invasive species (Martin et al., 2017). As noted above, range expansions are particularly interesting for macroimmunology, as each is an explicit spatial and temporal process. Considering this joint variation, spatial patterns in immunity could be most evident in seasons when food is limited or when abiotic conditions are harsh (Nelson & Demas, 1996). For example, work on red deer immunity found that spatial patterns in antibody concentrations varied substantially across seasons (Albery et al., 2018).

Although incorporating seasonality into macroimmunology may not always be feasible given trade-offs between spatial and temporal sampling, we also implore researchers to consider time when standardizing efforts over space. Spatial patterns can be obscured,

or artificially produced, if sites are sampled at different months or years or use different protocols (Plowright et al., 2019). For ecoimmunology, factors such as the time between capture and sampling and time between sample collection and assays can also introduce additional noise (Becker, Czirják, Rynda-Apple, & Plowright, 2018; Zylberberg, 2015). For macroimmunology, we thus encourage spatial sampling at a uniform timepoint or conducting spatiotemporally coordinated field studies.

A broader concern in ecoimmunology is whether variation in immunity corresponds to a host's ability to clear infection or to past or current infection state (Bradley & Jackson, 2008). Several studies highlighted in this review demonstrate that spatial studies can differentiate the effect of parasite pressure from those of abiotic or biotic conditions when data on both predictors exist (e.g. Cornet et al., 2009; Couch et al., 2008; Table 1). However, it is often unclear whether to target a priori parasites known to exert selective pressures, which can introduce bias if these parasites have locally gone extinct in a host population. Alternatively, metagenomic assays can quantify parasite diversity more broadly (Edwards & Rohwer, 2005). Although the costs of metagenomics remain high when applied to individual hosts, macroimmunology studies could pool samples by site to generate a spatial metric of parasite pressure (Bergner et al., 2019). Such less-biased data on spatial parasite diversity could be included with other environmental covariates to assess their relative contribution to shaping spatial variation in immune defence. This approach would be especially informative for testing whether latitudinal gradients in immunity simply reflect latitudinal gradients in parasite pressure or other biogeographic factors.

Similarly, ecoimmunology has moved from attempting to quantify 'immunocompetence' to measuring multiple functional responses (Demas, Zysling, Beechler, Muehlenbein, & French, 2011). The development of sequencing and transcriptomic technologies now allows profiling immune gene expression via single gene and genomic approaches (Fassbinder-Orth, 2014). Such advances have been adopted by macroimmunology, as studies most often tested spatial variation in immune genes with qPCR, MHC diversity, and RNA-Seq. Systems approaches could also provide less reductionist measures of how the environment is associated with immunological traits (Martin et al., 2016).

Traits such as resistance and competence are difficult to measure directly but provide the most effective insights about defence (Downs, Adelman, & Demas, 2014). Most immune measures included in our synthesis are likely to reflect resistance or competence; tolerance, the ability to minimize effects of parasites on fitness, has rarely been explored spatially. In one key example, house finches in areas with a longer history of *Mycoplasma gallisepticum* presence showed greater tolerance than birds in areas with no exposure (Adelman, Kirkpatrick, Grodio, & Hawley, 2013). Such work, alongside theory on resource variation and tolerance (Budischak & Cressler, 2018), highlights the need for future work in this area and to assess whether spatial variation in exposure has consistent effects. Alongside quantifying spatial parasite diversity,

future studies on the macroecology of tolerance would also benefit from assessing spatial variation in parasite load (Burgan, Gervasi, Johnson, & Martin, 2019). Additionally, validations of biomarkers for these traits can facilitate more direct interpretations of how defence varies spatially. For example, a captive study of house sparrows exposed to West Nile virus assessed whether resistance or tolerance could be predicted with cytokines. Higher constitutive expression of a pro-inflammatory cytokine predicted shorter infectious periods (indicating stronger resistance), whereas greater expression of an anti-inflammatory cytokine was associated with improved tolerance (Burgan, Gervasi, & Martin, 2018). Validation of biomarkers for such traits would improve inference in macroimmunology.

The experimental validation of biomarkers for resistance and tolerance also highlights just one of several complementary areas between large-scale studies and more focused, small-scale studies of immunity and environmental variation. We see macroimmunology as playing an important role in developing hypotheses for field experiments and captive studies that triangulate on causal inference (Plowright, Sokolow, et al., 2008). In particular, large-scale field studies could fit into prior research programs for developing model systems in ecoimmunology, where researchers first obtain extensive information about host-parasite interactions and immune phenotypes before identifying reliable biomarkers (Pedersen & Babayan, 2011). Following such foundational work, a cross-sectional macroimmunology study could identify the scale of spatial dependence in immunity across a broad site gradient and identify environmental covariates with high importance. Subsequently, one could set up a focused field manipulation or longitudinal study within a smaller, more logistically feasible number of sites that span the identified range of environmental variation. For example, a macroimmunology study that identifies latitudinal range limits as a key predictor of immune phenotypes, rather than elevation or any geographic range edge (Ardia, 2007; Becker, Nachtmann, et al., 2019), could direct longitudinal work to capture seasonal variation across several sites at the core, northern, and southern parts of a distribution. A common garden study of individuals from the core and latitudinal edge populations could further assess the degree to which observed differences represent genetic variation or phenotypic plasticity. In such an approach, prior work on house sparrows showed that immune differences between two temperate and tropical house sparrow populations persisted in captivity, suggesting that latitudinal variation reflects more than acclimation to different habitats (Martin, Pless, Svoboda, & Wikelski, 2004). Similarly, large-scale studies that identify urbanization as a key determinant of immunity (e.g. Fokidis et al., 2008) could be followed by field experiments to further differentiate the roles of improved food availability from other ecological factors such as infection or population size (Pedersen & Greives, 2008). Longitudinal studies could establish tolerance differences between habitat contrasts (e.g. recapture rates of infected hosts), while captive studies could use parasite challenge to test for fitness effects between populations (Corby-Harris & Promislow, 2008).



### 5.3 | Macroecological approaches for data synthesis

These methodological suggestions could help generate a larger and more robust body of data on spatial determinants of immunity. We lastly encourage the application of macroecological approaches to reveal generalities in how environmental variation relates to immune defence (Martin et al., 2018; Stephens et al., 2016). Machine learning algorithms hold particular promise, given their ability to accommodate heterogeneous datasets and high degrees of collinearity (Hochachka et al., 2007). Boosted regression trees could facilitate deriving the importance of environmental covariates collected across diverse spatial scales (e.g. Brock et al., 2019) to immunological data within and between studies and taxa. Furthermore, clade-based methods such as phylogenetic factorization, which can identify taxonomic groups at various phylogenetic scales that most differ in species-level data, could identify which host clades show consistent relationships between spatial covariates and specific immune phenotypes (Washburne et al., 2019). Future applications could assess the degree to which spatial autocorrelation in immunity (e.g. range parameters from correlograms, global Moran's  $I$ ) displays phylogenetic signal. Such taxonomic patterns could be applied to guide taxa-dependent spatial sampling designs.

Advances in meta-analysis relevant to ecology and evolution (Nakagawa & Santos, 2012) could also help reveal general relationships between environmental conditions and immunity while controlling for phylogenetic relatedness between host species, methodological variation and spatial proximity of studies. Our systematic review did not quantitatively synthesize effect sizes for the relationships between spatial covariates and immunity, given the current limitations in spatial replication and analysis. However, future application of meta-analytic methods could test general support for several of the questions posed as research priorities. For example, a recent meta-analysis of forest degradation had an overall moderate effect size with immune outcomes (Messina et al., 2018). Additional meta-analyses could further test how particular immune axes (e.g. innate or adaptive), measures of function (e.g. BKA) or whole-organism traits (e.g. tolerance) generally respond to latitude, whether these trends are driven by parasite richness and how relationships may vary by taxa. With sufficient data across geographies and species, similar meta-analyses could assess general patterns in how range expansions affect investment in inflammation rather than humoral defence. Meta-analyses of urbanization could assess whether these habitats enhance innate defence or facilitate a general upregulation of immunity or how greater isolation of urban hosts (and lower genetic diversity within populations; Miles, Rivkin, Johnson, Munshi-South, & Verrelli, 2019) affects immune response and diversity. Such analyses could provide novel and generalizable insights into the spatial drivers of defence.

## 6 | CONCLUSIONS

Macroecology holds promise as an approach to identify the drivers of spatial variation in wildlife immune defence. Future work on the

host taxa and priority questions emphasized here, alongside opportunities posed by coupling large-scale field studies with small-scale field experiments and longitudinal approaches as well as applying large-scale data synthesis, could facilitate scaling ecoimmunology from individual- to habitat-level perspectives. Such work could provide new insights into the environmental drivers of defence while also facilitating novel opportunities to predict infection risks in the context of climate change (e.g. through latitudinal gradients), range expansions and biological invasions, and land conversions (e.g. urbanization and habitat loss).

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### AUTHORS' CONTRIBUTIONS

D.J.B. designed the synthesis and organized data collection; D.J.B., G.F.A., C.A.F., M.K.K. and T.J.L. collected the data; D.J.B. analysed the data; and all authors contributed to writing the manuscript and provided critical feedback.

### DATA AVAILABILITY STATEMENT

Data are available in the Dryad Digital Repository: <https://doi.org/10.5061/dryad.s7h44j134> (Becker, Albery, et al., 2019).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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