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Host genetic diversity limits parasite success beyond agricultural systems: a meta-analysis

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There is evidence that human activities are reducing the population genetic diversity of species worldwide. Given the prediction that parasites better exploit genetically homogeneous host populations, many species could be vulnerable to disease outbreaks. While agricultural studies have shown the devastating effects of infectious disease in crop monocultures, the widespread nature of this diversity–disease relationship remains unclear in natural systems. Here, we provide broad support that high population genetic diversity can protect against infectious disease by conducting a meta-analysis of 23 studies, with a total of 67 effect sizes. We found that parasite functional group (micro- or macroparasite) affects the presence of the effect and study setting (field or laboratory-based environment) influences the magnitude. Our study also suggests that host genetic diversity is overall a robust defence against infection regardless of host reproduction, parasite host range, parasite diversity, virulence and the method by which parasite success was recorded. Combined, these results highlight the importance of monitoring declines of host population genetic diversity as shifts in parasite distributions could have devastating effects on at-risk populations in nature.

1. Introduction

Most natural populations are genetically diverse [1]. Given there is often specificity between hosts and parasites [2], host population genetic diversity is thought to increase the chance that one or more individuals is resistant to infection. The likelihood of a parasite encountering a susceptible host is thus reduced [3]. Genetically homogeneous host populations are conversely predicted to be more vulnerable to infection, given the uniformity of host susceptibility. This negative relationship between host genetic diversity and parasite success is often referred to as the 'monoculture effect' [4].

The study of the monoculture effect in agricultural settings is extensive [5–7]. A recent meta-analysis showed that with increased diversity in intraspecific cultivar mixtures, disease presence is reduced and crop yields increased [7]. However, crop plants are under artificial selection for high yield, and may therefore exhibit less genetic polymorphism than hosts in the wild. We consequently know little of the extent to which low genetic diversity influences parasite success across species and environments beyond agricultural contexts.

Threats to within-species genetic diversity are on the rise. There is evidence that habitat alterations, pollution and global temperature changes, as well as the restriction of species geographical ranges, may lead to increased genetic drift and reduced population genetic diversity [8,9]. Impacts of humans on local species biodiversity, however, remain controversial [10,11]. Populations with reduced genetic diversity might suffer diminished evolutionary potential [12] and increased inbreeding depression [13,14]. Knowing whether there is an additional threat of outbreaks in these populations is crucial for disease management and species conservation approaches.

Theory has illuminated the dynamics of parasite spread [4,15–18] in diverse host populations as well as examined the level of diversity required to stop

transmission [19,20]. However, whether population genetic diversity can impact parasite success in nature more broadly remains unclear for several reasons. First, given that parasite transmission can be determined by host density [3], the relative effects of density versus host genetic diversity need to be elucidated [20]. Shrinking habitats, for example, can result in higher population densities (and lower resource availability) where parasites can transmit better due to more contact between hosts [21,22]. Second, even when focusing on host genetic diversity alone, there is great variation across systems in the conditions under which infection and diversity are measured. In comparison to diverse populations, genetically homogeneous bumblebee (*Bombus terrestris L.*) populations, the microsporidian *Nosema bombi* has higher success, but the trypanosomelid *Crithidia bombi* does not [23]. In other cases, we see an increase in parasite success on the homogeneous host populations when multiple parasite species infect [23–26] but not always between one host–parasite species pair [27,28]. Third, because parasite success is measured differently across studies, and even within systems, there is the potential that the relevant measure of parasite success is not used. For example, in honeybee (*Apis mellifera*) host populations, genetic diversity has a negative impact on parasite success when infection prevalence or parasite load is measured, but not always when host survival is calculated [29]. Host survival might be less informative because the interplay of virulence, force of infection and the timing of infection might determine the overall spread of pathogens in host populations [30]. It is therefore unclear whether the effect of low host genetic diversity on parasite success is relevant to host–parasite interactions in non-agricultural systems across the tree of life.

We tested the effect of host population genetic diversity on parasite success with a formal meta-analysis across a range of host–parasite systems. We searched the published literature for all publicly available data sources and compared the effects of low and high host genetic diversity on parasite success using Hedges's effect size g (with positive values indicating an effect of low host genetic diversity on parasite success) with a nested random mixed effects meta-analysis model. We also tested whether biological traits associated with the species in the interaction, as well as study settings and measures, could explain variation in the effects of genetic diversity on parasite success.

2. Material and methods

(a) Literature search

In July 2019, the literature was searched using keyword searches on Web of Knowledge, Google Scholar and PubMed, with a subset of the terms 'host genetic diversity', 'low versus/and high host genetic diversity', 'heterogeneous versus/and homogenous host populations', 'monoculture effect', 'disease spread' and 'parasite prevalence' to investigate the effect of low versus high host population diversity on parasite disease impact (see electronic supplementary material, figure S1 for PRISMA flowchart [31] summarizing study collection process). We gathered data of parasite success in host populations of varying genetic diversity. We define 'parasite success' as any measure of a parasite's ability to proliferate within a host population reported in a given study. As parasite presence within a host population is measured differently across studies, the following terms were included as measurements of parasite success: parasite load, parasite virulence, parasite abundance, host mortality rate, viral concentrations, viral load, infection rate and infection intensity. We also checked reference lists for other potential papers. Studies were also searched for and extracted from review papers.

Papers were included in this study if they met the following inclusion criteria:

(i) The study was published in a peer-reviewed academic journal.
(ii) The study collected parasite success data from two distinct comparable host population groups with any measured difference in diversity, such as low versus high genetic diversity, inbred versus outbred, and monoculture versus polyculture.
(iii) In the study, both host population groups contained the same species.
(iv) The study measured genetic diversity at the host population level and not community diversity or individual-level genetic heterozygosity.
(v) The study was not conducted in an agricultural system.
(vi) The study did not interfere with parasite or host life cycle, as in passaging manipulations.

We excluded agricultural studies as a recent meta-analysis had already demonstrated the benefits of intraspecific diversity to crop yields (and thus host fitness) in the presence of infectious disease [7].

(b) Statistical analysis

We calculated Hedges's g from studies using the method described in Hedges [32]. This is a standard and widely used method of calculating effect sizes in meta-analyses which takes into account small sample sizes [33,34]. To calculate effect size g, the mean parasite measurements and their standard deviation for each treatment were extracted in the order of low host population diversity and high host population diversity. We extracted data from either paper figures, reported statistics in the text, or raw data received from authors. Where means and standard deviations in each group were not available (2 out of 23 studies), t-values and degrees of freedom were extracted.

We calculated the standard mean differences using the *escalc* function in the package *metafor* in R v. 3.6.0 (R Development Core Team) before performing a nested random mixed effects meta-analysis model using the *rma.mv* function. We chose this model to account for the fact that we collected several effect sizes per study, where some studies shared the same host species, which has the potential for pseudo-replication and phylogenetic non-independence. Estimates of effect size g were extracted from the model. We first tested for an overall relationship between host population genetic diversity and parasite success using the entire dataset. We then tested whether the magnitude of the relationship was dependent on the following moderator variables: study setting, parasite success measure, host reproduction, parasite functional group, parasite's host range, parasite diversity and ability of parasite to cause host death (see electronic supplementary material, table S1 for variable definitions). The measure of heterogeneity of moderator variables was reported as Cochran's Q test, where Q is the weighted sum of squares about the fixed effect estimate between subgroups [35].

We tested for an effect of both study setting (field or laboratory-based environments) and parasite success measure on the relationship between host genetic diversity and parasite success. For the latter, we separated measures into three groups based on those used in studies included in the meta-analysis: parasite prevalence, parasite load and host mortality (electronic supplementary material, table S1). Studies looking at overall parasite presence in a host population were placed under the

category 'parasite prevalence'. Where measures of parasite propagules per host were taken, studies were placed under 'parasite load'. Measures of mortality within a population were placed under 'host mortality'. In order to incorporate studies publishing survival data, measures of host mortality were taken as the inverse of published survival measures.

We then focused on the impact of host and parasite biological traits on variation in the magnitude and direction of effect sizes. We first considered host reproductive mode, given sexual and asexual strategies can generate disparate levels of population genetic diversity. However, one study was placed under a separate reproduction group as the host (*Daphnia magna*) had undergone both sexual and asexual reproduction in the study. Second, we looked at infection by parasite functional group (micro- or macroparasites) as the former tends to be associated with higher mortality [36], and third, the parasite's host range (1 host species or greater than 1 host species), as this factor has been shown to have an impact in crop studies [37,38] due to the reduced genetic specificity between hosts and multi-host parasites. Fourth, we separated studies into three categories—one genotype of one parasite species (1 genotype), multiple parasite genotypes of one parasite species (greater than 1 genotypes), and multiple parasite species (greater than 1 species)—to determine whether the diversity–disease relationship was dependent on parasite diversity. Higher levels of parasite diversity might increase the pool of susceptible hosts in a diverse population. Lastly, we tested whether effect sizes were dependent on the parasite's ability to cause host death. Compared to less harmful parasites, virulent parasites could select for greater levels and variation of resistance in the host population.

(c) Assessing for potential publication bias

Studies that report larger effects are more likely to get published in comparison to studies reporting smaller effects [34]. To check for publication bias, we visualized the spread of our effect sizes by creating a funnel plot (electronic supplementary material, figure S2). We then performed a fail-safe n analysis to calculate the number of additional studies needed to reduce the significance level of the weighted average effect size [39].

3. Results

We found 32 unique host–parasite interactions in 23 papers containing data that followed the inclusion criteria. Papers often included results from multiple experiments or exposures to multiple parasite species. A total of 67 effect sizes were retrieved from this dataset, covering a diverse range of host and parasite species (table 1).

After the construction of a funnel plot, we find no indication of a publication bias in this meta-analysis dataset, with the majority of points falling symmetrically within the plot (electronic supplementary material, figure S1). The unusual shape of the plot can be explained by the fact that small sample sizes were predominantly found in laboratory studies, whereas large sample sizes were predominantly found in field studies. Consequently, studies with large sample sizes had higher errors than those with small sample sizes explaining the shape of the plot (we highlight this by colourising the plot by study setting). Rosenberg's fail-safe n analysis showed that an additional 604 studies would need to be added to reduce the significance level of this meta-analysis.

Our results are consistent with the hypothesis that low host genetic diversity results in higher parasite success ($g = 0.3527$, $p < 0.0001$; figure 1*a*). We found that the effect size is influenced by study setting ($Q = 9.2111$, d.f. = 1, $p = 0.0024$; figure 1*b*), where the magnitude of the effect size is significantly greater for field studies ($g = 0.7003$) in comparison to laboratory studies ($g = -0.5249$). Parasite success measures used in the studies do not significantly influence the effect size ($Q = 2.6526$, d.f. = 2, $p = 0.2655$; figure 1*c*).

We found no evidence of an effect of host reproduction on the direction or magnitude of the effect size ($Q = 4.0711$, d.f. = 2, $p = 0.1306$; figure 2*a*), even when we excluded the Daphnia study by Altermatt & Ebert [40] ($Q = 0.9147$, d.f. = 1, $p = 0.3389$). Conversely, we found that the effect size was dependent on parasite functional group ($Q = 8.3621$, d.f. = 1, $p = 0.0038$, figure 2*b*). The success of microparasites ($g = 0.6277$), and not macroparasites ($g = -0.1725$), was limited by high host population genetic diversity. Neither the direction nor magnitude of the effect size was influenced by host range ($Q = 0.2864$, d.f. = 1, $p = 0.5925$; figure 2*c*), parasite diversity ($Q = 3.1047$, d.f. = 2, $p = 0.2118$; figure 2*d*) or whether parasites caused host mortality ($Q = 3.5504$, d.f. = 1, $p = 0.0595$; figure 2*e*).

4. Discussion

Our meta-analysis shows that host population genetic diversity reduces parasite success across multiple natural systems. In particular, we find that host population genetic diversity is effective at limiting microparasite infection success, with little to no effect on the macroparasites tested, and the protection is stronger when measured in the field. Our findings additionally highlight the potential damage that emerging infectious diseases may have on genetically homogeneous host populations.

The parasites included in our meta-analysis were highly variable in terms of their host range. However, we found no evidence that a parasite's host range affected its success in host populations of low or high genetic diversity. Indeed, we see evidence of resistance in more diverse populations involving highly specialized interactions [40,68,71], in broad-spectrum interactions at the genotypic level [55] and in those that cross host species boundaries [25,26,72]. That host range is not a factor here is in contrast with those results found in crop studies. For example, in rusts and powdery mildews, disease severity is driven by a pathogen's host specificity [6]. The mirroring of parasite virulence genes to host resistance genes means that crop mixtures need to contain both susceptible and resistant cultivars to avoid a monoculture effect. When there is a lack of host specificity, mixed cultivar populations are just as susceptible as monocultures. For example, mixed cultivar populations have been observed to be slightly more susceptible to infection [37] or completely susceptible [38] in comparison to monocultures to the fungal pathogen *Mycosphaerella graminicola*. These findings suggest that the threat to crops from generalist parasites is greater than specialist parasites.

Given that host range did not influence whether parasite success was reduced by host genetic diversity, it is possible that novel parasites, just as well-adapted parasites, could have high success in host populations with low genetic diversity. Essentially, homogeneous populations could be vulnerable to outbreaks with spill-over or emerging infectious diseases which are less likely to be host specific [73], but for which there is clearly genetic variation for resistance. The resistance to emerging parasites in these cases could be due to historical contact or similar mechanisms of infection applied by parasites with an evolutionary history to the

Table 1. Summary of the literature on the effect of host population genetic diversity on measures of parasite success across host–parasite systems.

source paper	paper number	host	measure of host diversity	parasite	host range (ref.)	parasite type	infection measure	data source	data extracted	*n* effect sizes
Altermatt & Ebert [40]	1	*Daphnia magna*	1 versus 10 genotypes	*Octosporea bayeri*	1 host species [40]	fungus	parasite load	fig. 2, raw data	mean ± s.d.	2
Baer & Schmid-Hempel [23]	2	bumblebee (*B. terrestris*)	queens inseminated with sperm from 1 versus 2 or 4 males	*Crithidia bombi, Nosema bombi*	>1 host species [66]	protozoa, fungus	parasite load	fig.ure 1, raw data	mean ± s.e.	4
Baer & Schmid-Hempel [24]	3	bumblebee (*B. terrestris*)	queens inseminated with sperm from 1 versus 2 or 4 males	*Crithidia bombi*	>1 host species [66]	protozoa	parasite load, parasite prevalence	fig. 1, raw data	mean ± s.d.	4
Baer & Schmid-Hempel [25]	4	bumblebee (*B. terrestris*)	queens inseminated with sperm from 1 versus 2 or 4 males	*Crithidia bombi*	>1 host species [66]	protozoa	parasite load, parasite prevalence	raw data	mean ± s.d.	4
Calleri *et al.* [42]	5	termite (*Zootermopsis angusticollis*)	inbred versus outbred	*Metarhizium anisopliae*	>1 host species [62]	fungus	parasite load	in text	mean ± s.d.	1
Desai & Currie [29]	6	honeybee (*A. mellifera L.*)	queens inseminated with sperm from 1 versus 12 drones	*Varroa destructor*, deformed wing virus, black queen cell virus, Israeli acute paralysis virus	>1 host species [57,69,70]	mite, virus, virus, virus	parasite load, host mortality, parasite prevalence	figs. 1, 2, 4, 5, 7 and 8	mean ± s.e.	11
Ganz & Ebert [47]	7	*Daphnia magna*	1 versus 10 genotypes	*Glugoides intestinalis*, *Ordospora colligate*, *Microsporidium sp.* (undescribed species)	1 host species [79] and >1 host species [79]	fungus, fungus, fungus	parasite prevalence	fig. 2	mean ± s.e.	3
Hale & Briskie [49]	8	New Zealand robin *(Petroica australis)*	bottleneck versus source population	hippoboscid flies (*Ornithomya spp.* and *Ornithoica* spp.), feather mite	>1 host species [67]	fly, mite	parasite load	fig. 1	mean ± s.d.	2
Hughes & Boomsma [51]	9	ant *(Acromyrmex echinatior)*	1 patriline versus 3 patrilines	*Metarhizium anisopliae* (strain KVL 02–73)	>1 host species [62]	fungus	host mortality	fig. 4	mean ± s.e.	2
Liersch and Schmid-Hempel [52]	10	bumblebee (*B. terrestris*)	full sister workers versus mixed workers	*Crithidia bombi*, *Nosema bombi*, *Apicystis (Mattesia) bombi*	>1 host species [66,76]	protozoa, fungus, protozoa	parasite prevalence, parasite load	fig. 1	mean + CI	2
Manlik *et al.* [54]	11	bumblebee (*B. terrestris*)	island versus land population	*Nosema bombi*	>1 host species [66]	fungus	parasite prevalence	in text	mean ± s.e.	1
Pearman & Garner [55]	12	italian agile frog (*Rana latastei*)	low versus high population genetic variability	*Ranavirus* (frog virus 3)	>1 host species [55]	virus	host mortality	fig. 2, raw data	mean ± s.d.	3

(*Continued.*)

Table 1. (*Continued.*)

source paper	paper number	host	measure of host diversity	parasite	host range (ref.)	parasite type	infection measure	data source	data extracted	*n* effect sizes
Reber *et al.* [27]	13	ant (*Formica selysi*)	monogynous versus polygynous colonies	*Metarhizium anisopliae*	>1 host species [62]	fungus	host mortality	figs. 1 and 2	mean ± s.e.	3
Schmidt *et al.* [28]	14	ant (*Monomorium pharaonis*)	inbred versus mixed colonies	*Beauveria bassiana*	>1 host species [62]	fungus	host mortality	fig. 3	mean + CI	3
Seeley & Tarpy [56]	15	honeybee (*A. mellifera L.*)	queens inseminated with sperm from 1 versus 10 drones	American foulbrood (*Paenibacillus larvae*)	>1 host species [80]	bacteria	parasite prevalence	fig. 2, raw data	mean ± s.d.	2
Shykoff & Schmid-Hempel [58]	16	bumblebee (*B. terrestris*)	1 genotype versus 3 genotypes	*Crithidia bombi*	>1 host species [66]	protozoa	parasite prevalence	fig. 2	*t*-value	2
Smallbone *et al.* [59]	17	guppy (*Poecilia reticulata*)	inbred versus outbred	*Gyrodactylus turnbulli* (strain Gt3)	>1 host species [77]	worm	parasite load	fig. 2	mean ± s.e.	1
Strauss *et al.* [61]	18	*Daphnia dentifera*	1 genotype versus 3 genotypes	*Metschnikowia bicuspidata*	>1 host species [79]	fungus	parasite prevalence	fig. S1B	mean ± s.e.	1
Tarpy [63]	19	honeybee (*A. mellifera L.*)	queens inseminated with sperm from 1 versus multiple drones	chalkbrood disease (*Acosphaera apis*)	>1 host species [83]	fungus	parasite prevalence	fig. 2	mean ± s.d.	1
Tarpy & Seeley [65]	20	honeybee (*A. mellifera L.*)	queens inseminated with sperm from 1 versus 10 drones	sacbrood (Iflavirus genus), chalkbrood disease (*Acosphaera apis*), European foulbrood (*Melissococcus plutonius*), American foulbrood (*Paenibacillus larvae*)	>1 host species [78,80,83,84]	virus, fungus, bacteria, bacteria	parasite prevalence	in text	*t*-value	4
van Houte *et al.* [68]	21	*Pseudomonas aeruginosa*, *Streptococcus thermophilus*	1 genotype versus 6, 8, 12, 24, and 48 genotypes and 1 genotype versus 44 genotypes	bacteriophage (DMS3), bacteriophage (2972)	1 host species [81,82]	virus, virus	parasite prevalence	fig. 2, raw data	mean ± s.d.	5
Wargo *et al.* [71]	22	rainbow trout (*Oncorhynchus mykiss*)	inbred versus outbred	infectious haematopoietic necrosis virus (IHNV) isolates: 220 : 90 (HV), WRAC 039-82 (LV), FF020-91 (B), FF030-91(C)	1 host species [71]	virus	parasite prevalence	fig. 2, raw data	mean ± s.e.	4
Whiteman *et al.* [26]	23	Galapagos hawk (*Buteo galapagoensis*)	inbred versus outbred	*Colpocephalum turbinatum*, *Degeerialla regalis*	>1 host species [48]	louse, louse	parasite load	fig. 2, raw data	mean ± s.d.	2

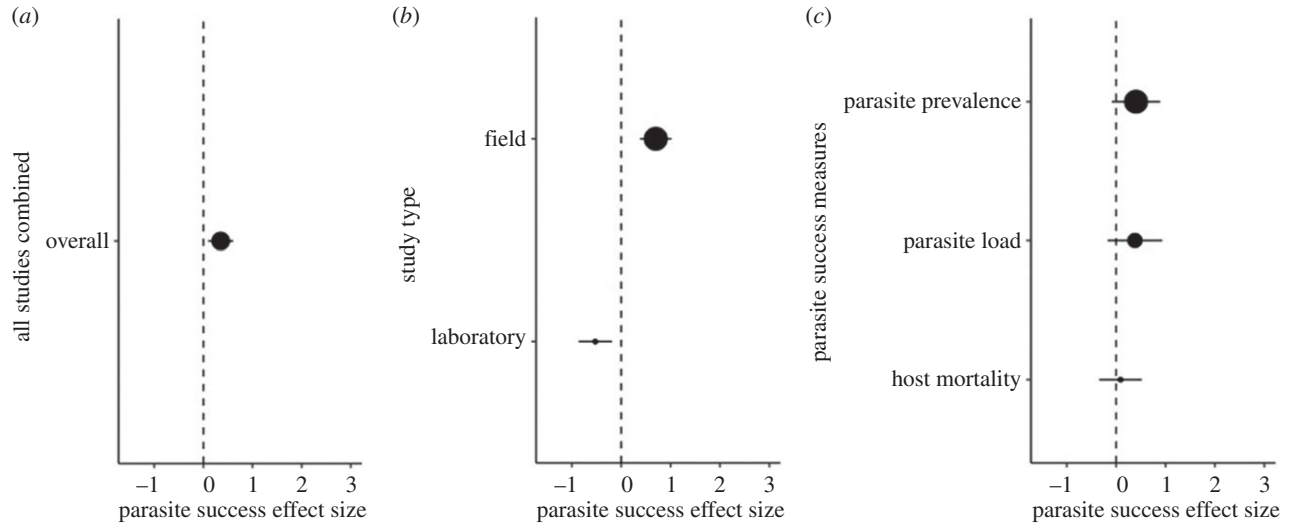

Figure 1. Impact of study setting on the effect of host genetic diversity on parasite success. Positive values indicate that low host genetic diversity has an impact on parasite success (i.e. a negative association between genetic diversity and parasite success). Negative values represent the opposite relationship. At an effect size of zero (dashed line), there is no relationship between host genetic diversity and parasite success. (*a*) Overall effect size ($n = 67$). (*b*) Moderator analysis of study type between field ($n = 36$) and laboratory ($n = 31$) studies. (*c*) Moderator analysis of parasite success measures between parasite load ($n = 19$), parasite prevalence ($n = 35$) and host mortality ($n = 13$). The size of the dot corresponds to the sample size. Effect sizes are shown with 95% confidence intervals.

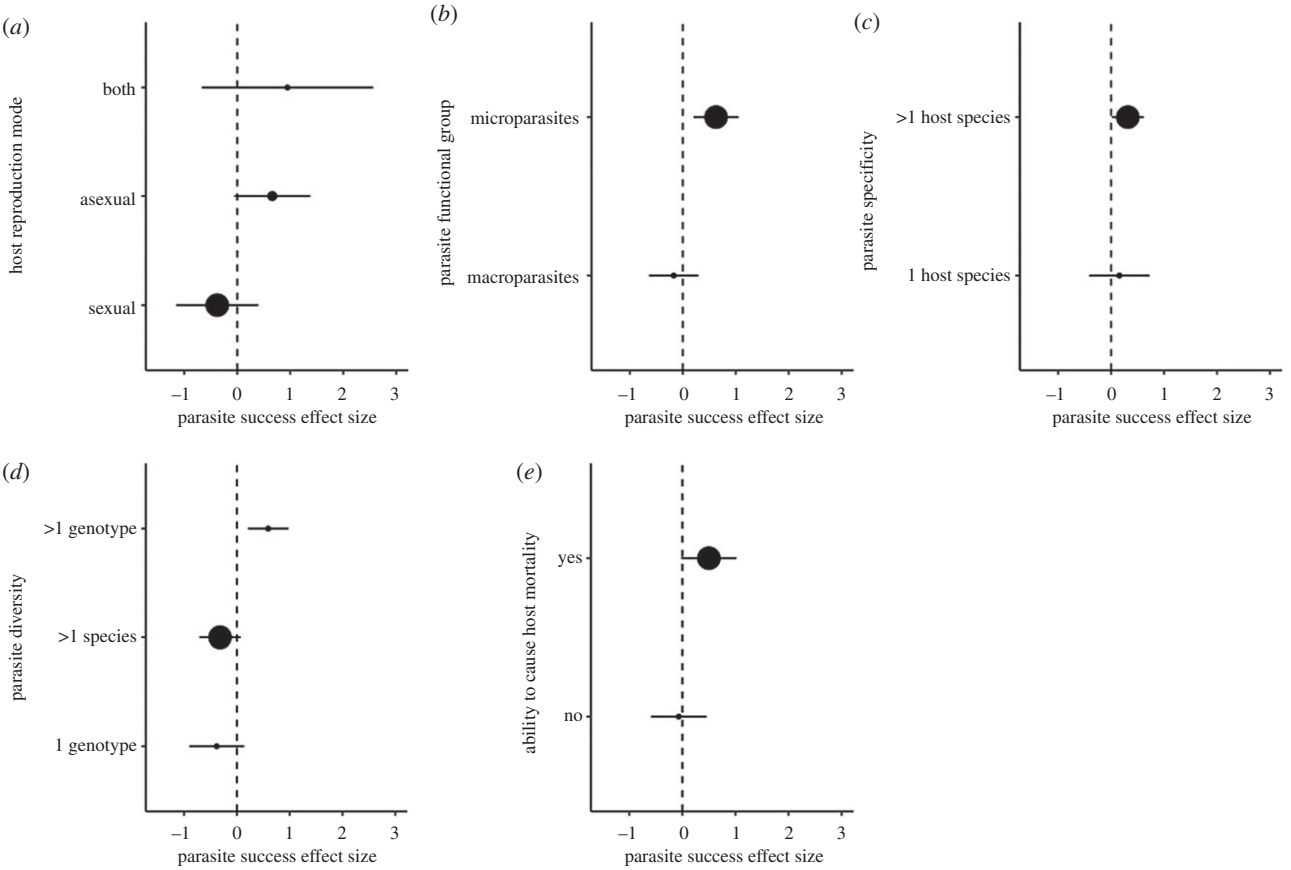

Figure 2. Impact of host and parasite characteristics on the effect of host genetic diversity on parasite success. Positive values indicate that low host genetic diversity has an impact on parasite success (i.e. a negative association between genetic diversity and parasite success). Negative values represent the opposite relationship. The dashed line (effect size of zero) represents no relationship between host genetic diversity and disease spread. Moderator analysis of (*a*) host reproduction mode: asexual ($n = 5$), both ($n = 2$) and sexual ($n = 60$) effect sizes, (*b*) parasite functional group between microparasite ($n = 57$) and macroparasite ($n = 10$) effect sizes, (*c*) host range between 1 'host species' ($n = 13$) and greater than 1 'host species' ($n = 54$) effect sizes, (*d*) parasite diversity, greater than 1 genotype ($n = 15$), greater than 1 species ($n = 37$) and 1 genotype ($n = 15$) effect sizes, and (*e*) the ability of a parasite to cause host death, displayed as yes ($n = 57$) and no ($n = 10$) effect sizes. The size of the dot corresponds to the sample size. Effect sizes are shown with 95% confidence intervals.

host [8]. Nevertheless, this result is concerning from a conservation perspective as global climate change has the potential to reduce within-species genetic diversity [74] and alter host population ranges [9,41]. Natural movement of individuals between populations has always served to bolster host diversity [9], and introducing new genotypes is an approach applied by conservation biologists to improve population viability [14]. While adding individuals to a population could

increase diversity and reduce inbreeding [43], a risk may be that new individuals, new species and changes in ecological opportunities bring in new parasites to the population [44,45]. There is potential here for an increased overlap between host populations with low genetic diversity and novel infections. Given that we found a stronger effect in field studies, these consequences are of real concern.

The difference in parasite success between diverse and homogeneous host populations was more pronounced in field studies, compared to laboratory studies, despite the additional environmental noise data collection in nature might involve. One reason could be that less diverse populations in the wild are more susceptible to infection than they are in the laboratory for reasons unrelated to genetic diversity. Hosts on islands as well as social insects, such as bees [65], ants [51] and termites [42], live in tight proximities to each other making parasite transmission easier in homogeneous populations. The stronger effect in field studies highlights the importance of the maintenance of diversity in natural populations.

In our meta-analysis, the success of macroparasites was not impeded by genetic heterogeneity in host populations. The macroparasites in the studies included herein were all ectoparasites, and their biology may explain our result. Ectoparasite transmission is often dependent on host-to-host contact [46,48], and thus host density is probably a critical factor in parasite success [46]. Host density may play a more important role than host genetic diversity here such that similarly aggregated populations varying in diversity might be equally susceptible to infection. It has been shown that the clustering of captive animal populations restricted by movement or wild animal populations restricted by ranges are highly vulnerable to ectoparasites [44,50]. Moreover, host social behaviours, such as grooming [29] or preening [26], can reduce ectoparasite success. In fact, in populations where social grooming is correlated with relatedness, ectoparasite load is dramatically reduced in highly related individuals [53]. Taken together, host diversity on its own does not always explain a reduction in parasite success, particularly in the case of ectoparasites.

Understanding the impact of host population genetic diversity on parasite infection outside of agricultural systems is crucial because of anthropogenic threats to the diversity of wild populations. This meta-analysis reveals that the susceptibility conferred by low host genetic diversity is a widespread phenomenon in nature, with microparasites most likely to encounter resistance in diverse host populations. Indeed, these broad patterns show that genetic diversity is a robust weapon against infection, similar to the effects of species biodiversity [60]. Our findings suggest that further erosion of within-species genetic diversity could drive outbreaks of both coevolving and emerging infectious diseases. Conservation efforts should focus on preserving population genetic diversity in vulnerable populations to improve their ability to fight off infections.

Data accessibility. Data available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.c856930 [75].

Authors' contributions. A.K.E.E. and K.C.K. conceived and designed the study. A.K.E.E. gathered the data and performed the statistical analysis with C.R.-M. A.K.E.E. and K.C.K. wrote the paper.

Competing interests. The authors have no competing interests.

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