Title: The effect of host population genetic diversity on variation in metrics of parasite success

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ABSTRACT

Conventional wisdom suggests that populations with lower levels of genetic diversity are at a greater risk of the more harmful effects of disease. However, previous attempts to qualify this proposition have focused on measuring the mean, rather than the variability, in metrics of parasite success. Since the ability of host population genetic diversity to limit the spread of disease requires some specificity between hosts and parasites, and the benefits of host population genetic diversity in resistance to infection may depend on the respective parasite population genetic diversity, we propose a diversity-uncertainty model which predicts that the mean and variability in parasite success depend on a combination of host range and parasite population genetic diversity. By re-analyzing a dataset combining 48 studies collected by previous meta-analyses, we show that the effect of host population genetic diversity reduces the mean success of single-host, but not host generalist, parasites. We find evidence for our original hypothesis that the variability of parasite success depends on a combination of host population genetic diversity, parasite population genetic diversity and host range. Together, these results challenge conventional wisdom and have important implications for how genetic diversity can be better managed in host populations.

INTRODUCTION

It is commonly believed that host populations with lower genetic diversity are at a greater risk of experiencing higher parasite success (i.e. disease (1)). This refers to the population-level prevalence (proportion of infected hosts), virulence (parasite-induced loss of fitness) or parasite load (average parasites per host (2–4)).

Previous studies of the generality of this proposed 'conventional wisdom' (1), have often focused on measuring the mean, rather than the variability, of parasite success (5,6). This is surprising, considering the importance of parasitic extremes, in terms of epidemics and whether they cause mass extinction (7,8), the predictably of recurrent bouts of disease across years and the repeatability of disease experiments in general. As a result, the relationship between host diversity and variability in parasite success is poorly understood (9). However, it is central to our ability to protect against future emerging diseases (10).

The implications of host community, species or genetic diversity on infectious diseases is often referred to as 'disease dilution' (11–15), the diversity-disease hypothesis (16–18) or the monoculture effect (19–23). This can be caused by an increase in individual host susceptibility (24), or a variety of population-level effects such as reducing the rate of encounter between susceptible and infectious individuals (encounter reduction), reducing the probability of transmission given an encounter (transmission reduction), decreasing the density of susceptible individuals (susceptible host regulation), increasing the recovery rate (recovery augmentation), or increasing the death rate of infected individuals (infected host mortality) (for a review, see (14)).

Although the exact mechanism is unclear, the negative relationship between host population genetic diversity and disease spread is often attributed to encounter reduction (25). Specifically, assuming that there is some level of matching (or genetic specificity (26)) required for a successful infection to occur (*sensu* matching alleles

model [MAM] (27)), there should be a lower chance of a parasite encountering a susceptible host as it spreads through a more diverse host population. Since the strength of genetic specificity varies across different host-parasite systems (27), we might expect that the effect of host population diversity on parasite success depends on the level of specificity for infection.

In theory, the effects of host population diversity on parasite success may also depend on the level of parasite diversity (28,29). For example, if there is a high level of genetic specificity for infection (*sensu* MAM), then we might expect host populations composed of a single genotype to be entirely susceptible to a single parasite genotype, which is much more likely to occur in a population with a high level of parasite diversity (28,29). One empirical study in a *Daphnia* host-parasite system found that the benefits of host genetic diversity for resistance to infection were reliant on a high level of parasite diversity (30).

Therefore, if we assume that there is a high level of genetic specificity for infection (*sensu* MAM) and both host and parasite populations are characterized by either high or low levels of genetic diversity, we can predict the following patterns for both the mean and variability in parasite success (Table 1):

A) Low host x low parasite population genetic diversity (Table 1A): We predict that there will be a high level of variability in parasite success, due to the host population being composed entirely of susceptible, or resistant, host genotypes, and an intermediate level of mean parasite success (determined by the overall frequency of resistant cf. susceptible populations).

B) High host x low parasite population genetic diversity (Table 1B): We predict that there will be a low level of both mean parasite success and variability in parasite success, due to the consistency of hosts to resist infection through a reduced encounter rate with matching parasite genotypes.

C) Low host x high parasite population genetic diversity (Table 1C): We predict that there will be a high level of mean parasite success and a low level of variability in parasite success, due to the consistency of parasite transmission through an enhanced encounter rate with matching host genotypes.

D) High host x high parasite population genetic diversity (Table 1D): We predict that there will be an intermediate level of both mean parasite success and variability in parasite success, due to the diverging effects of host and parasite genetic diversity leading to an inconsistent encounter rate between matching host and parasite genotypes.

Collectively, these predictions form our 'diversity-uncertainty' model for predicting the mean and variability of parasite success across populations with different levels of host and parasite diversity. This builds on previous work (31), which focused on the relationship between population diversity and variability in parasite-induced host mortality and pathogen abundance for only three out of the four possible combinations in Table 1, without also acknowledging the influence of the genetic specificity for infection on these hypotheses.

To test our diversity-uncertainty model, we examine the relationship between host population genetic diversity, parasite population genetic diversity and variability in parasite success for different levels of a proxy for genetic specificity using meta-analysis. After confirming the results of previous studies (5,6), which found a significant difference in mean parasite success between various host populations with high versus low genetic diversity, we then extend their analysis to a study of variability using a suite of different moderator variables.

In particular, we compare the difference in the variability of parasite success between host populations with high versus low genetic diversity using a combination of host

range and parasite population genetic diversity variables. Since the requisite population-level genetic specificity data does not exist for all of the combined studies, and MAM dynamics are more likely to rely on coevolution between a single host and parasite species compared to GFG, due to being driven by negative frequency-dependent selection (32), we assume that there is a relatively higher level of genetic specificity for parasites with a narrow host range (1 species) compared to parasites with a broad host range (> 1 species). On the other hand, we do not make any predictions about the mean level of, or level of variability in, parasite success for systems with a low genetic specificity for infection.

Overall, we find that the relationship between host genetic diversity and both the mean level of, and level of variability in, parasite success depends on a combination of host range and parasite genetic diversity.

Table 1. Our 'diversity-uncertainty' model. This shows the expected effects of host and parasite population genetic diversity on i) the mean (μ) and ii) the variability (σ) of parasite success for highly specific host-parasite systems (e.g. matching-allele model for infection genetics).

	Low diversity parasite	High diversity parasite
Low diversity host	A) Medium μ High σ	C) High μ Low σ
High diversity host	B) Low μ Low σ	D) Medium μ Medium σ

METHODS

Summary

We combined the data from two previous meta-analyses (5,6), which compared the standardized mean difference (SMD) in parasite success between host populations with qualitatively 'high' versus 'low' levels of genetic diversity, to calculate the log coefficient of variation ratio (lnCVR). In other words, we calculate the mean difference and ratio of variation in parasite success between host populations with different levels of genetic diversity. Across all the studies we include these replicates are sometimes experimental replicates in a lab, sometimes multiple natural populations, and sometimes repeated measures on single populations along a time series.

Data collection

The data collection for each control versus treatment comparison, which was later used in calculating effect sizes, involved five main steps (Figure 1):

1) First, we combined the list of studies from (5) and (6), removed any duplicate studies and added the data used to calculate the effect size, SMD, and its sampling variance in the original studies (mean, standard deviation, sample size), the metric of parasite success and the unique study, experiment and replicate identifiers used to account for the non-independence of separate effect sizes. We did not use the parasite success data from (6) because the original data extracted from each study was missing from their online supplementary material, so we would be unable to check the accuracy of their data during validation (step 3), so we extracted the replicate or population summaries from the data ourselves after step 3 and recalculated the mean, standard deviation, sample size etc. ourselves.

In addition, the data used to calculate Fisher's z (an effect size for the difference between two correlation coefficients) for the observational field studies from (5), was not in the correct format to calculate either SMD or lnCVR. Therefore, we did not include this information (from multiple populations with a continuous measure of

154 genetic diversity) at this stage and instead extracted the data ourselves and
155 recalculated it during steps 4 and 5. Also, we excluded any plant (wild or agricultural)
156 host data because a more detailed analysis of the plant literature would require a
157 separate review and we did not want to add effect size data for studies we already
158 knew were going to exclude during the next step.

159 2) Second, we amended the original study inclusion criteria (Table SX) and removed
160 any studies, experiment or comparisons which did not meet these criteria:

161 (i) 'Parasite success', which we define as the ability of a parasite to spread among
162 hosts (transmission rate, infection rate, prevalence), replicate on / within hosts (macro
163 / microparasite load, disease severity) or kill hosts (virulence i.e. host survival /
164 mortality rate) was measured among replicate populations across time or space.

165 (ii) Parasite success data was collected from two or more host populations with a
166 difference in genetic diversity, such as the level of relatedness among individuals
167 (inbred versus outbred), genotypic diversity (high versus low) or heterozygosity.

168 (iii) Genetic diversity was quantified at the host population level and not community
169 diversity or individual-level genetic heterozygosity.

170 (iv) The study focused on an animal (or bacterial) host species.

171 (v) The study does not re-analyze the data from a previously published study.

172 (vi) The parasite success data was not replicated simply by using an alternate way of
173 measuring host population diversity.

174 (vii) An attempt to take the parasite success data from clearly illegible figures was not
175 made.

176 3) Third, we checked the accuracy of the data from the excel spreadsheets used to
177 calculate the summary of the parasite data for each control and treatment group (5).

There were 11 studies, 13 experiments and 27 comparisons which did not match the published raw data (available in the main text or online or in the supplementary material of each publication), 3 studies, 8 experiments and 32 comparisons which were calculated wrong and 4 studies, 5 experiments and 10 comparisons which had not been transferred from the excel spreadsheets into the final metadata file correctly. Therefore, we fixed any errors in how the parasite success data was calculated, annotated the data correctly with the corresponding information and removed any data which was incorrect. Admittedly, there was one study which we could not check, because the original data was sent by personal communication from (33) to (5), but we included it in our analysis anyway.

4) Fourth, we collected any data we had removed by going back to the original publications and extracting the data from the main text or supplementary files (we used PlotDigitizer (https://plotdigitizer.com/) for any figures). This included 26 studies which met our inclusion criteria, but were removed because they were either missing the replicate-level raw data (6) or they were observational field studies based on multiple populations with a continuous measure of genetic diversity (5), 11 studies, 13 experiments and 27 comparisons which we removed because they did not match the published data, 4 studies, 5 experiments and 10 comparisons which were removed because they were annotated incorrectly, and additional data for 3 comparisons (34–36) that were not made in the original analysis by (5).

We also collected information on 10 different moderators (for why, see Table 2) by standardizing or recoding existing moderator variables used by (5), including host range, parasite diversity, metric of parasite success, host species, parasite type, source of host genetic diversity, scale of host diversity, mode of host reproduction, whether the parasite induces host mortality and whether the study was performed in a laboratory environment. Note that parasite diversity was categorized as high if it was collected from a natural population for a lab study, part of an observational or

experimental field study, or if more than one genotype had been identified (but this only applied to a small number of comparisons) or low if it was a laboratory strain of a parasite or only one genotype had been identified (but again, this only applied to a small number of comparisons). Where the information on these moderator variables was not already available from the supplementary material of (5) and was not available in the published article, we either performed a general search online, using Google, or a more detailed search on the Web of Science database if this information was not readily available.

5) Fifth, we calculated the mean, standard deviation and sample size for each comparison of control and treatment groups from the data we extracted, as well as the data calculated incorrectly in the previous analysis by (5). In total, this included 36 studies, 56 experiments and 130 comparisons.

For studies based on multiple populations with one or more continuous measures of genetic diversity, (33,35,37–55), we chose the measure of genetic diversity which was the best reflection of population-level genetic diversity (such as a measure based on a Hardy-Weiberg equilibrium) and split the populations into two even groups of high diversity and low diversity, before finally calculating a pooled mean, standard deviation and sample size for each control and treatment group. Similarly, for studies with multiple control groups (34,56), we calculated a pooled mean, standard deviation and sample size. For studies which measured host survival, this was converted into host mortality to better reflect parasite success.

After finishing all five steps of data collection, there was enough parasite success data to calculate both the SMD and lnCVR for 211 non-independent comparisons of a group of control versus treatment host populations.

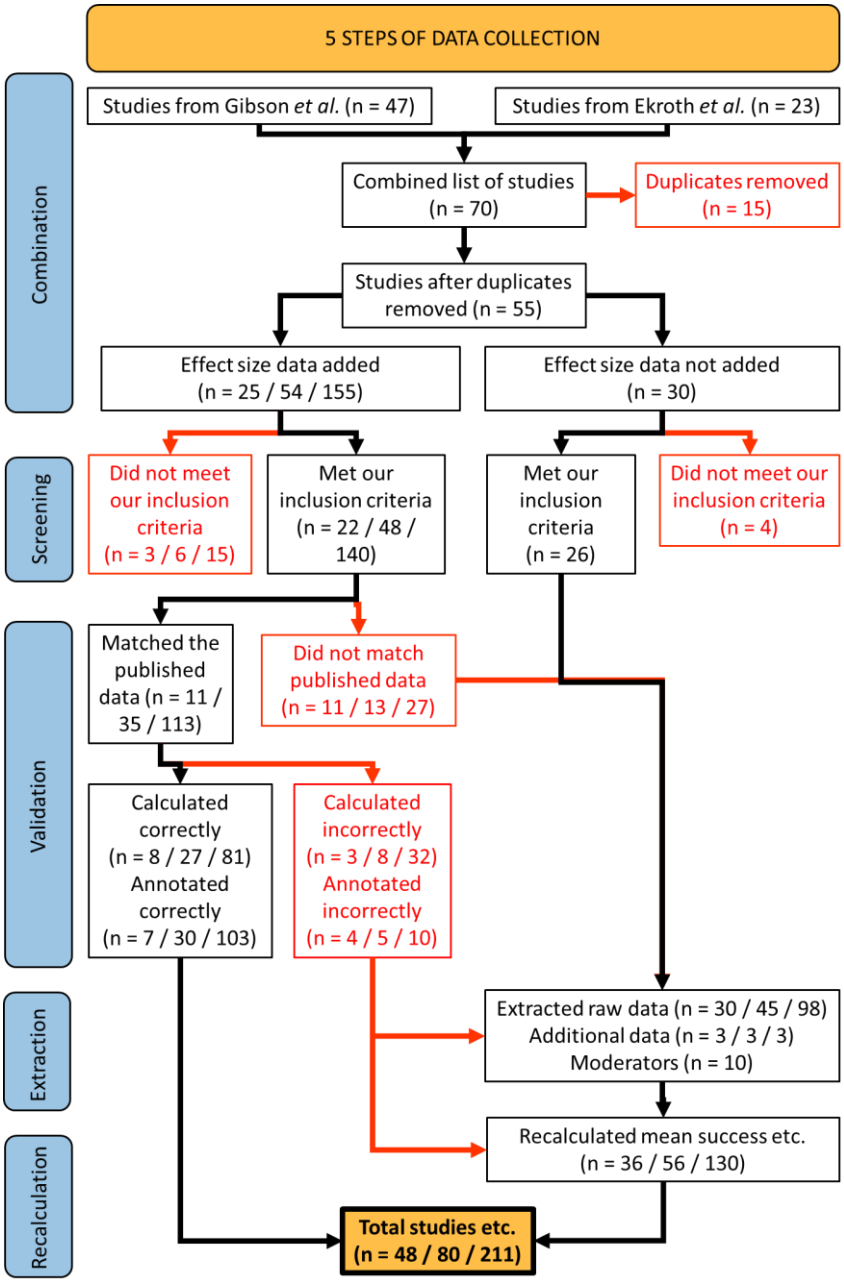

Figure 1. How data was collected for each control versus treatment comparison of parasite success, which was later used in calculating effect sizes. n = number of studies / experiments / comparisons (the multi-level structure of the data make it appear that some sums are incorrect). Adapted from the preferred reporting items for systematic reviews and meta-analyses (PRIMSA) statement (57).

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Calculation of effect sizes (SMD, lnCVR, lnRR, lnVR)

We calculated two main effect sizes (standardized mean difference [SMD] and log coefficient of variation ratio [lnCVR]) and two additional effects sizes (log response ratio [lnRR] and log variability ratio [lnVR]) to test the robustness of our results. Please note that all calculations of effect sizes and any subsequent calculations in this paper were performed in R v4.3.2 (58).

Main effect sizes - We chose SMD and lnCVR as our main effects sizes because they compare the difference in either the mean or variability of two groups whilst accounting for certain factors: (i) SMD measures the mean difference between two groups (high versus low diversity) in terms of standard deviations (59,60), so it can be used to compare different ways of measuring the same outcome (prevalence, load and virulence) (61), and uses a correction for small sample sizes, which is a common feature of ecological studies (62). (ii) lnCVR measures the ratio of variability between two groups adjusted for the size of the group means (63) and as a result, accounts for the possibility that the magnitude of the variability may scale with the mean, as is the case for many types of count data (such as parasite load) that follow a Poisson distribution.

Alternative effect sizes - We calculated lnRR and lnVR as alternatives to our main effect sizes, and although they did not account for all of the same factors, still measured the same difference in the mean and variability between two groups (63,64). Therefore, we were able to test the robustness of our results by comparing these two sets of effect sizes (65).

Before calculating our effect sizes, we added a small value (0.001) to the mean and standard deviation in parasite success for each pair of control and treatment groups to avoid any errors when taking logs of these data. For consistency, we calculated SMD and its sampling variance from the formula derived from the supplementary material of

(5), and calculated all variability effect sizes and their sampling variances using the code from (63), as these were not used in the previous meta-analyses discussed above (5,6), and instead are unique to our analysis. We calculated lnRR using the escalc function from the metafor package v4.4.0 (66) because it was not clear how this was calculated in (5). To account for comparisons based on shared controls, we calculated the variance-covariance matrix for each effect size, using the make_VCV_matrix function from the metaAidR package v0.0.0.9000 (67).

Publication bias

Before analyzing the data fully, we calculated the overall effect sizes for SMD and lnCVR and tested for any potential publication bias using funnel plots and Egger's regression (68).

Meta-analytic models were fitted to the data using the rma.mv function from the metafor package v4.4.0 (66). We included fixed effects for each type of effect size, the variance-covariance matrix of sampling errors, standard random effects for study and host genus, and correlated random effects for comparisons taken from the same experiment. Standard random effects for study and host genus were used to account for the possibility of non-independence between experiments originating from the same study and potential correlations between effects from closely related host species. Similarly, correlated random effects were used to account for potential non-independence of comparisons taken from the same experiment (multiple timepoints for a single comparison of control and treatment groups, or effect sizes from the same group of populations based on different measures of parasite success).

Funnel plots were used to identify whether published effect sizes were evenly distributed around model means by examining how outcomes varied as a function of their precision (standard error). This was achieved from a visual inspection of these plots and statistical evaluation using Egger's regression.

Meta-analysis of overall data

To test whether there was a significant difference in mean parasite success (SMD) or the variability in parasite success (lnCVR) between host populations with high versus low genetic diversity, we fitted mixed effects meta-analytic models. All of the models used in this paper were based on the same structure as those used for testing the presence of publication bias.

Context dependence

Partial moderator analysis - To test if the overall effect of host population genetic diversity on the mean and variability in parasite success depended on an interaction between host range and parasite genetic diversity, we introduced an interaction term for these two moderators in our original meta-analytic models. Therefore, we could compare:

1) High versus low single-host parasite population genetic diversity.

2) High versus low multi-host parasite population genetic diversity.

We compared the significance level of each individual predictor within the model, as well as the contrasts between them using the *glht* function from the *multcomp* package v1.4.25 (69).

Full moderator analysis – To test our additional hypotheses (Table 2) for the eight remaining moderator variables, we modelled each moderator separately with its own individual mixed effects model. Before running the models, we removed redundant moderator categories with a limited sample size, such as transmission or infection rate (versus prevalence) and disease severity (versus load) for the metric of parasite success, and prokaryotic (versus vertebrate or invertebrate) for host species.

307 We compared the significance level of each individual predictor within the model, as
308 well as the contrasts between them using ANOVA with a correction for multiple
309 comparisons (Holm's method).

310

311 Table 2. Hypotheses for additional moderators.

Moderator	Hypothesis
Metric of parasite success	Our study of 'parasite success' combined data of several types (eg prevalence, virulence, infection load). Using this moderator, we tested if the effects of host population genetic diversity differed between these different metrics.
Host species	The effect of host population genetic diversity may be influenced by the specificity of genetic interactions between host and parasite. These genetic interactions are thought to be more specific in invertebrates than in vertebrates (70), therefore we tested for inconsistency of the host population genetic diversity effect in these two groups.
Parasite type	Since microparasite infections tend to be short-lived, whereas macroparasites are usually long-lasting, it is generally believed that they can withstand the host immune response (71). This suggests that they might not be as tightly coevolved, and have a lower genetic specificity for infection, than microparasites. Therefore, we tested for inconsistency of the host population genetic diversity effect in these two groups.
Source of host genetic diversity	Studies typically investigate the impact of host genetic diversity by either (i) inbreeding lineages to create a comparison between inbred and outbred populations, (ii) selecting a suite of wildtype genotypes for controlled experiments with either low genetic diversity or high genetic diversity, or (iii) sampling organisms from the wild from populations that have been characterised as having different levels of genetic diversity. We used this moderator to test if these different sources of genetic diversity affected the influence of host population genetic diversity.
Scale of host diversity	Host populations were predetermined as having either high or low diversity (discrete) or we separated them into such categories as part of our data collection (Fig. 1, step 5) because they used multiple populations with a continuous measure of diversity. We used this moderator to test if this feature of how studies were designed had an effect on the influence of host population genetic diversity.
Mode of host reproduction	Host species reproduced sexually, asexually or using a combination of the two (i.e. facultatively sexual, such as *Daphnia*). We used this moderator to test if these different modes of host reproduction affected the influence of host population genetic diversity.
Host mortality?	The range of parasites studied can be further categorized by how virulent they are. Therefore, we used this moderator as a proxy for how virulent the parasites were, in terms of whether or not they kill the host, to test if

	differences in parasite virulence affected the influence of host population genetic diversity.
Laboratory?	We used this moderator to test if the difference in study setting (laboratory versus field) affected the influence of host population genetic diversity.

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313 *Sensitivity analysis of overall effects*

314 To test the robustness of our results for the combined (overall) dataset, we performed
315 a series of 'leave-one-out' sensitivity analyses. This involved the iterative exclusion of
316 either one independent comparison (i.e. treatments with shared controls were
317 considered grouped together into a single comparison) or study at a time.

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319 RESULTS

320 *Absence of publication bias*

321 Our dataset contained 211 estimates of the effect that changes in host population
322 genetic diversity have on parasite success; we assessed this effect on both mean
323 parasite success (SMD) and the variability in parasite success (lnCVR). Visual
324 inspection of the funnel plots for the effect of host population diversity on mean parasite
325 success (Fig. 2A) and its effect on the variability in parasite success (Fig. 2B), showed
326 no evidence for publication bias. More stringent evaluation showed that there was no
327 correlation between the size of the effects themselves and their standard error (Egger's
328 test for both SMD and lnlnCVR: R = 0.06, 95% CI [-0.24, 0.37], p = 0.67 and R = -0.03,
329 95% CI [-0.38, 0.32], p = 0.86 respectively).

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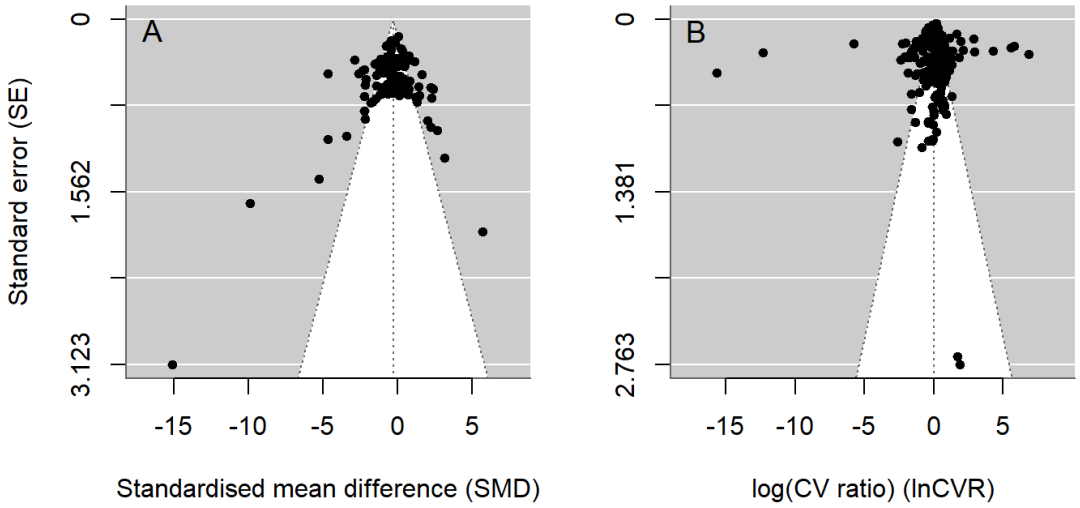

Figure 2. Testing for publication bias: the distribution of published effect sizes for our meta-analysis as a function of their precision (standard error). The x-axis in both plots shows effects of an increase in host population genetic diversity (high vs low) for A) the mean difference in parasite success (SMD) and B) the ratio of variation in parasite success (lnCVR). Model means and their 95% confidence intervals are shown by the dashed black lines.

331
332 *Evenly distributed animal host and parasite taxa*

333 Our dataset included a diverse range of hosts and parasites, including 31 unique host
334 genera, 60 unique parasite genera and 71 (92) unique host-parasite genera (or
335 species) combinations.

336 The distribution of unique host taxa was biased towards animals (invertebrate and
337 vertebrate genera / species), with only two unique non-animal (prokaryotic) host
338 species (Table 3). However, there was an even distribution of the unique parasite taxa
339 across the combination of all unique host taxa.

340 Table 3. The number of unique host and parasite combinations and how evenly they
341 are distributed across different taxonomic groups. The number of unique combinations

342 of host and parasite genera and species is shown by the first two numbers separated
343 by a backslash (genera / species) and the number of studies they correspond to in
344 parentheses. The total number of studies is higher than 48 (the total number of studies
345 in our dataset), because there were some studies with multiple comparisons of unique
346 host and parasite combinations. The colour coding is based on the number of unique
347 combinations of host and parasite genera.

		Host taxon			
		Prokaryote	Invertebrate	Vertebrate	Total
Parasite taxon	Animal	0 / 0 (0)	12 / 14 (6)	10 / 13 (8)	22 / 27 (14)
	Bacteria	0 / 0 (0)	2 / 2 (2)	13 / 16 (5)	15 / 18 (7)
	Fungi	1 / 1 (1)	15 / 18 (16)	1 / 1 (1)	17 / 20 (18)
	Protozoa	0 / 0 (0)	7 / 12 (11)	3 / 3 (2)	10 / 15 (13)
	Virus	1 / 1 (1)	3 / 7 (2)	4 / 4 (4)	7 / 12 (7)
	Total	1 / 2 (2)	39 / 53 (37)	31 / 37 (20)	71 / 92 (59)

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350 *Overall effect of host population genetic diversity on mean parasite success is negative*

351 There was a significant effect of host population genetic diversity on mean parasite
352 success (SMD = -0.29, 95% CI = [-0.57, -0.02], n = 211; Fig. 3A), which shows that
353 there is a negative relationship between host population genetic diversity and the mean
354 parasite success. However, the effect of host population genetic diversity on the
355 variability of parasite success was not significant (lnCVR = 0.02, 95% CI = [-0.30, 0.35],
356 n = 211; Fig. 3B), which suggests that there is no relationship between host population
357 genetic diversity and the variability in parasite success.

358 In these analyses the residual variation (heterogeneity) in the data for both the
359 difference in the mean and variability of parasite success was high (I^2 = 84.0% & 82.0%
360 respectively). Most of this variation was explained by the effect of study (84.0% &
361 80.7%) and only a small amount was explained by host genus (0.0% & and 3.3%).

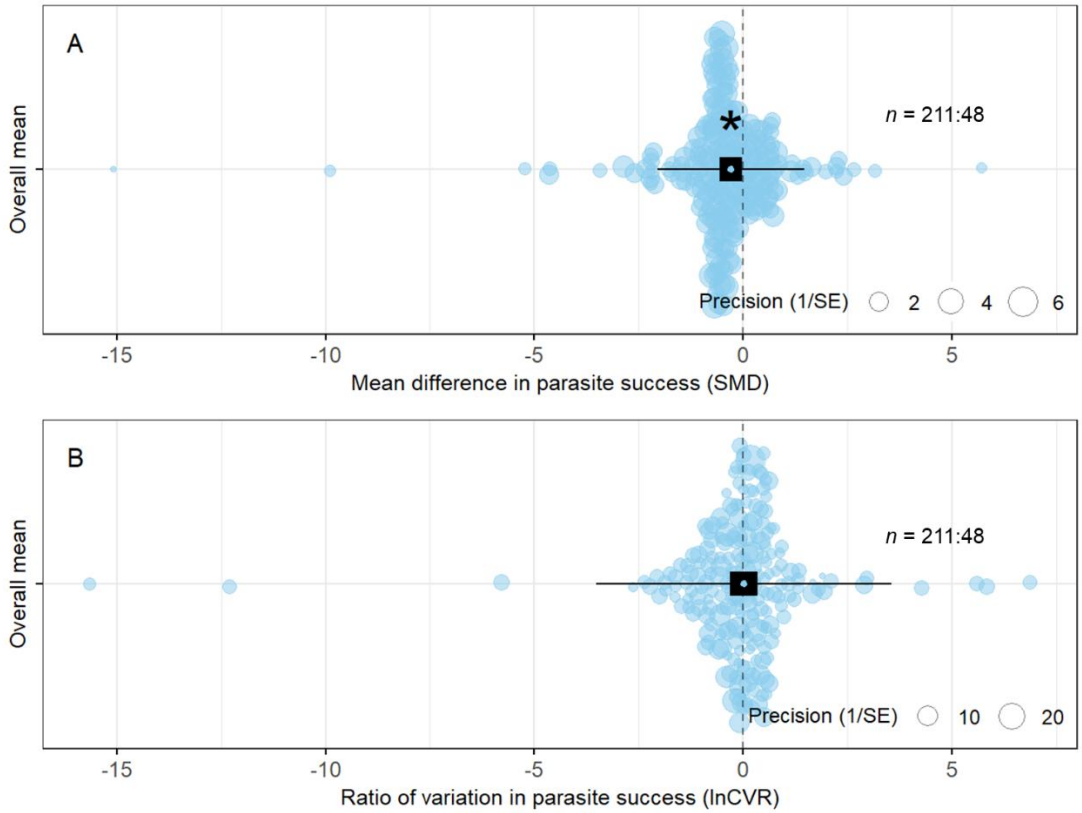

Figure 3. Overall effect of host population genetic diversity on the mean and variability in parasite success. The x-axis in each plot shows the effect of increasing host population genetic diversity on either A) the difference in mean parasite success (SMD) or B) the difference in the variability in parasite success (lnCVR). The dashed line indicates an effect size of zero where there is no influence of host population genetic diversity on parasite success. Model means are shown with 95% confidence intervals (thick black lines) and prediction intervals (thin black lines). Individual effect sizes (circles) are scaled according to the inverse of their standard error. n = sample size of the data (the number of effect sizes : the number of studies). Model means that are significantly different from zero are indicated by an asterisk ($p < 0.05$). Forest plot alternatives are shown in the online supplementary material (Fig. S1).

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364 *Variability in the success of single-host parasites depends on the combined host and*
365 *parasite population genetic diversity*

366 The overall conclusion that higher host population genetic diversity reduces mean
367 parasite success, but does not the affect the variability in parasite success, is relatively
368 simplified. In fact, there are significant effects of host population genetic diversity on
369 both the mean and variability in parasite success which depend on a combination of
370 parasite population genetic diversity and host range.

371 In contrast to the overall effect of host population genetic diversity on mean parasite
372 success, which was significantly negative (SMD = -0.29, 95% CI = [-0.57, -0.02], n =
373 211; Fig. 3A), separating the effects of host population genetic diversity by a
374 combination of parasite population genetic diversity and host range showed that the
375 effect of host population genetic diversity on mean parasite success was only
376 significant for single versus multi-host parasites.

377 In addition, although there was no overall effect of host population genetic diversity on
378 the variability in parasite success (lnCVR = 0.02, 95% CI = [-0.30, 0.35], n = 211; Fig.
379 3B), there was a significant difference in the effect of host population genetic diversity
380 on the variability in the success of singe-host parasites with low versus high population
381 genetic diversity (glht: p = 0.03; Fig. 4B). Specifically, increased host population
382 genetic diversity lead to either an increase or decrease in the variability of the success
383 of single-host parasites when their own population genetic diversity was either high or
384 low.

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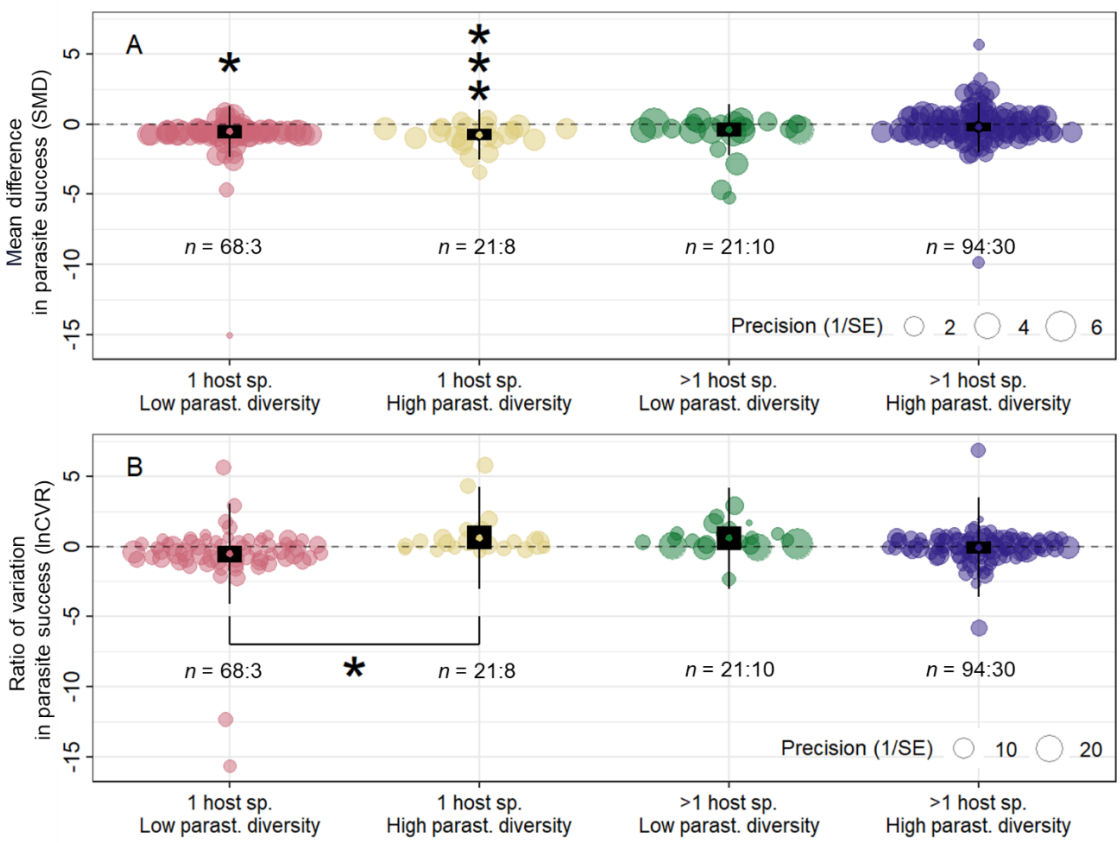

Figure 4. The influence of host range and parasite population genetic diversity on the effect of host population genetic diversity on the mean and variability in parasite success. The x-axis in each plot shows the effect of increasing host population genetic diversity on either A) the difference in mean parasite success (SMD) or B) the difference in the variability in parasite success (lnCVR). The dashed line indicates an effect size of zero where there is no influence of host population genetic diversity on parasite success. Model means are shown with 95% confidence intervals (thick black lines) and prediction intervals (thin black lines). Individual effect sizes (circles) are scaled according to the inverse of their standard error. n = sample size of the data (the number of effect sizes : the number of studies). The significance level of individual model means, as well as any pairwise contrasts, is indicated by one ($p < 0.05$) or three ($p < 0.001$) asterisks.

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Context-dependent effect of host population genetic diversity

To evaluate our table of hypotheses (Table 2), we investigated how eight other aspects of study design influenced the effect of host population genetic diversity on the mean and variability in parasite success (Fig. 5)

We found that the effect of host population genetic diversity was significantly negative on the mean success of microparasites (Fig. 5C), for inbred versus outbred hosts (Fig. 5D), for sexually reproducing hosts (SMD = -0.40, 95% CI = [-0.73, -0.07], p = 0.02, Fig. 5F), parasites which caused host mortality (SMD = -0.34, 95% CI = [-0.68, -0.00], p = 0.05, Fig. 5G) and non-lab based studies (SMD = -0.33, 95% CI = [-0.65, -0.01], p = 0.04, Fig. 5H). For the effect of host population genetic diversity on the variability in parasite success, we found that this was significantly negative for asexually reproducing hosts (Fig. 5N).

In addition, comparisons between specific levels of these moderators showed a highly significant difference in the mean difference in parasite success between micro- and macroparasites (QM = 13.2, df = 1, $p < 0.001$, Fig. 5C) and also a significant difference in the ratio of variability in parasite success between both sexual hosts and either asexual (QM = 6.40, df = 1, p = 0.01, Fig. 5N) or facultatively sexual hosts (QM = 5.53 df = 1, p = 0.02, Fig. 5N).

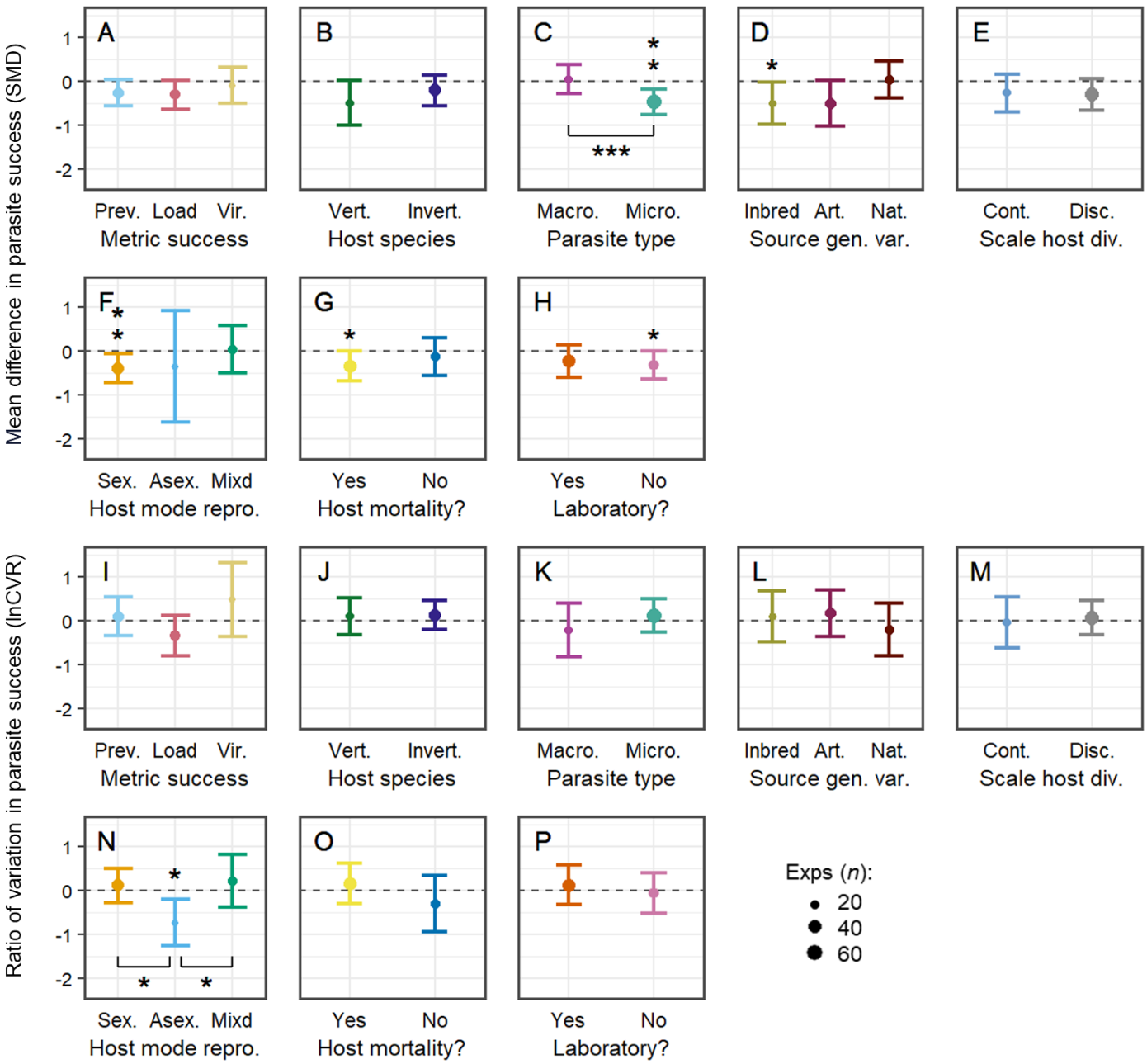

Figure 5. The context-dependence of the effect of host population genetic diversity on the mean and variability in parasite success. The x-axis in each plot shows the effect of increasing host population genetic diversity on either A) the difference in mean parasite success (SMD) or B) the difference in the variability in parasite success (lnCVR). Model means are shown with 95% confidence intervals and are scaled according to the number of experiments. The dashed line indicates an effect size of zero. The significance level of individual model means, as well as any pairwise contrasts, is indicated by one ($p < 0.05$), two ($p < 0.01$) or three ($p < 0.001$) asterisks. The following abbreviations are used; Prev. (Prevalence), Vir. (Virulence), Vert. (Vertebrate), Invert.

(Invertebrate), Macro. (Macroparasite), Micro. (Microparasite), Source gen. var. (Source of host genetic diversity), Art. (Artificial), Nat. (Natural), Scale host div. (Scale of host diversity), Cont. (Continuous), Disc. (Discrete), Host mode repro. (Mode of host reproduction), Sex. (Sexual), Asex. (Asexual), Mixd (Mixed).

Our results are robust to leaving data out, but require the right 'mean' effect size

To test the robustness our of results, we performed a suite of 'leave-one-out' sensitivity analyses and remodeled our parasite success data with an alternative set of effect sizes.

The suite of sensitivity analyses showed that the results of our main effects were not dependent on the inclusion of a particular study (Table 4., Fig. S2) or independent comparison in our dataset (Table 4., Fig. S3). However, they were less robust to using the log response ratio (lnRR) as an alternative effect size to the standardized mean difference (SMD) to measure to effect of host population genetic diversity on mean parasite success. Although both measures showed a negative effect of host population genetic diversity on mean parasite success, the alternate way of measuring this was not significant (lnRR = 0.93, 95% CI = [-0.40, 2.25], n = 211). In comparison, the alternate variability measure, the log variability ratio (lnVR), supported the result of the main effect size (the log coefficient of variation ratio, lnCVR) by showing that there was no significant effect of host population genetic diversity on the variability in parasite success.

Table 4. Results of the leave-one-out sensitivity analyses. To test the robustness of the results using our main effect sizes, we re-modelled the data using an iterative exclusion of either one study (Leave1studyout) or one independent comparison (Leave1trtout) and calculated the mean model estimate and the mean p-value across all the models. The following abbreviations are used; ES (effect size), SE (mean standard error across all models), ci.lb and ci.ub (mean lower and upper bounds of 95% confidence intervals across all models respectively).

Method	ES	Estimate	SE	z-value	p-value	ci.lb	ci.ub
Leave1trtout	SMD	-0.29	0.14	-2.07	0.04	-0.56	-0.02
Leave1trtout	lnCVR	0.02	0.17	0.13	0.9	-0.3	0.35
Leave1studyout	SMD	-0.29	0.14	-2.05	0.04	-0.57	-0.01
Leave1studyout	lnCVR	0.02	0.17	0.13	0.87	-0.31	0.35

DISCUSSION

Building on the recent studies by (5,6), we show that the conventional theory, which suggests that there is a negative effect of host population genetic diversity on mean parasite success, is not always correct (1). Although there is a benefit to high host population genetic diversity, which protects against mean parasite success, our moderator analysis shows that it strongly depends on the nature of the host-parasite association, such that the parasite success of host specialists, but not generalists, is affected. We propose that this is driven by the amount of genetic specificity for infection because specialist parasites could be more likely to have highly specific, matching-allele-type interactions between host resistance and parasite infectivity alleles.

The benefit of host population genetic diversity in protecting against the mean success of single-host, but not multi-host, parasites is an important distinction. It highlights the susceptibility of vulnerable host populations (small, fragmented populations with low genetic diversity) to infection by host-specific parasites, rather than infection by multi-host parasites. This represents a change of perspective that could help to protect vulnerable host populations by prioritizing how genetic diversity within these populations is managed (72) or even by finding a way to alter the genetic specificity of host and parasite associations to make them less specific, such as by introducing alternative hosts for the parasite.

We also found that the effect of host population genetic diversity on parasite success was highly context dependent. Using our partial moderator analysis, in which we modelled the interaction between parasite population genetic diversity and host range,

455 we showed the importance of our proposed diversity-uncertainty model (Table 1).
456 Specifically, increased host population genetic diversity lead to either an increase or
457 decrease in the variability of the success of single-host parasites when their own
458 population genetic diversity was either high or low.

459 This has big implications for identifying disease threats, such as epidemics, to host
460 populations. Our results show that the combination of low host and low parasite
461 population genetic diversity can sometimes lead to an extremely high level of parasite
462 success. However, the most vulnerable host populations are those with a combination
463 of low genetic diversity themselves and high parasite population genetic diversity
464 because there is a consistently high level of parasite success. In addition, the
465 protective effect of host population genetic diversity diminishes with increasing parasite
466 population genetic diversity, so we might want to prioritize the genetic diversity of low
467 host-high parasite genetic diversity associations.

468 Similarly, there are also consequences for the repeatability of disease experiments and
469 the predictability of recurrent disease outbreaks. We might expect that combinations
470 of 1) low host and parasite population genetic diversity and 2) high host and parasite
471 genetic diversity have the biggest implications for study repeatability because lab
472 experiments are likely to be low x low and field experiments are likely to be high x high.
473 Due to their high levels of variability, these systems will also have similar issues in
474 terms of predictability of future disease occurrence and emergence.

475 In conjunction with our partial moderators, our full moderator analysis highlighted
476 several other significant influences on the effect of host population genetic diversity on
477 parasite success, including parasite type, the source of genetic diversity, the mode of
478 host reproduction, whether or not host mortality is affected and whether or not the study
479 was performed in a laboratory. In particular, the effect of host population genetic
480 diversity on the mean success of microparasites was much stronger (more negative)

than macroparasites. This confirmed our original hypothesis, which suggested that macroparasites have a lower genetic specificity for infection due the longer-lasting nature of their infections and thus being less tightly coevolved with their hosts.

One of the other key moderators was the source of host population genetic diversity. This showed that there was a significant reduction in mean parasite success between inbred versus outbred hosts, but not between other host comparisons which had been established by selecting suites of unique genotypes or sampling organisms from wild populations. This result makes sense and may have occurred due to combination of an inbreeding effect, where inbred hosts are more susceptible to disease than outbred hosts (24), and population-level genetic diversity effects, which was not necessarily the case for the other categories of how host population genetic diversity was assembled.

Despite using the same set of moderators, our results were inconsistent with previous meta-analytic studies (5,6). They modelled each moderator separately (6) or using all possible combinations of different moderators and calculated model averages (5) and either found that most of their moderators had no significant influence, or a limited influence, on the effect of host population genetic diversity on mean parasite success. Specific differences between our moderator analysis to theirs include the use of a larger number of effect sizes, which meant we did not suffer a limited sample size in certain moderator categories as they did (e.g. single-host parasites and parasites with one or more strains), and the interaction between host range and parasite population genetic diversity, which was not included in one of these studies (6).

However, we temper the exciting nature of results with some considerations:

1) There is a large number of effect sizes (68) for single-host parasites with low population genetic diversity, but most of these actually come from a prokaryotic

bacterial host study (73), rather than a vertebrate or invertebrate host, which is the case for most of our data.

2) Host range may not be a reliable estimate of the genetic specificity for infection. This is because we based this on the prediction that highly specific interactions between host and parasite genotypes would be more likely for tightly coevolving pathogens (MAM), as we might expect between a single host and parasite species, compared to multiple hosts and a single parasite species with a broad host range.

3) The results of our moderator analysis rely on particular ways of labelling the data. For example, comparing mainly natural versus laboratory strains of parasites could be a poor indication of the effect of parasite population genetic diversity because the exact level of diversity was not actually quantified. Similarly, our measure of host range is somewhat subjective and based on an incomplete literature.

4) The suite of leave-one-out analyses showed that our overall effects, which did not include any moderators, were robust to the potential influence of extreme values from particular studies or data points, but the overall effect of host population genetic diversity on mean parasite success effect size relies on our use of the standardized mean difference versus the log response ratio (refer to the methods for why this was selected as an alternative effect size).

Our final thought is that most of our data concentrates on the effect of host population genetic diversity on both the mean and variability in parasite success for spatially replicated groups of host populations (except for one study (74)). We expect that the diversity-uncertainty model may also apply to the effect of host population genetic diversity on both the mean and variability in parasite success across time, but with some key differences. For example, repeated bouts of directional selection from parasite outbreaks can reduce host and parasite population genetic diversity through

time (75,76), which could increase the mean and reduce the variability in parasite success. However, the precise nature of selection and its resulting impact on host and parasite population genetic diversity depends on the underlying host-parasite infection genetics (i.e. MAM versus GFG (77)).

SUMMARY

In this study, we measured the difference in the mean and variability in parasite success between host populations with high versus low genetic diversity. First, we challenge so-called 'conventional wisdom' (*sensu* (1)) and propose a diversity-uncertainty model to better understand the context in which the effect of host population genetic diversity really matters for both the mean and variability in parasite success. We find that host population genetic diversity affects the mean success of host-specific parasites, but not host generalists, which could be a result of greater genetic specificity for infection. We then demonstrate that our diversity-uncertainty model is appropriate for our collection of studies, such that the effect of host population diversity on the variability in parasite success depends on a combination of parasite diversity and host range. Finally, we find that there are a number of other context dependent effects of host population genetic diversity on both the mean and variability in parasite success, such as parasite type. Overall, these findings represent a change of perspective that could help to protect vulnerable host populations by prioritizing how genetic diversity within these populations is managed. Future study of the diversity-uncertainty hypothesis across a range of plant host-parasite systems would help generalize these findings.

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DATA ACCESSIBILITY

Reviewer URL:

https://datadryad.org/stash/share/E2NqLZ8KL2oYaPQLSYatmNNIeUub3aeC4ExfjJvE5Hw

Data available from the Dryad Digital Repository: doi:10.5061/dryad.2bvq83bzq (78).

AUTHOR CONTRIBUTIONS

All authors discussed the results and contributed to the final manuscript. S.P. performed the data collection, analysed the data and wrote the manuscript. B.D. and M.T. contributed to the final version of the manuscript and supervised the project.

COMPETING INTERESTS

The authors have no competing interests.

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