

REVIEW

Does genetic diversity limit disease spread in natural host populations?

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It is a commonly held view that genetically homogenous host populations are more vulnerable to infection than genetically diverse populations. The underlying idea, known as the ‘monoculture effect,’ is well documented in agricultural studies. Low genetic diversity in the wild can result from bottlenecks (that is, founder effects), biparental inbreeding or self-fertilization, any of which might increase the risk of epidemics. Host genetic diversity could buffer populations against epidemics in nature, but it is not clear how much diversity is required to prevent disease spread. Recent theoretical and empirical studies, particularly in *Daphnia* populations, have helped to establish that genetic diversity can reduce parasite transmission. Here, we review the present theoretical work and empirical evidence, and we suggest a new focus on finding ‘diversity thresholds.’ *Heredity* (2012) **109**, 199–203; doi:10.1038/hdy.2012.33; published online 20 June 2012

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INTRODUCTION

It seems to be conventional wisdom that genetically homogeneous populations suffer from more severe pathogen outbreaks than diverse populations (Elton, 1958; Sherman *et al.*, 1988; Schmid-Hempel, 1998; Altizer *et al.*, 2003). Infection is more likely to be transmitted between genetically similar hosts (Anderson and May, 1986), and upon encountering resistant hosts, parasites would likely die, fail to successfully reproduce (Anderson and May, 1986), or otherwise be removed from the population (Keesing *et al.*, 2006). As such, the risk of infection, especially by virulent pathogens, may select for outcrossing over uniparental forms reproduction, such as self-fertilization or parthenogenesis (Jokela *et al.*, 2009; King *et al.*, 2009; Morran *et al.*, 2011), resulting in an overall increase in genetic diversity (King *et al.*, 2011). There may not seem to be an escape from disease, but genetic diversity in host populations may reduce the risk of infection.

The empirical link between disease spread and genetic diversity has its origin in agricultural research. Agricultural fields represent environments in which plants are selected for high yield, and may therefore exhibit less genetic polymorphism than those in the wild. It is well known that disease epidemics have devastated agricultural monocultures (for example, rice blast, Zhu *et al.*, 2000), and that monocultures are typically more susceptible to outbreaks than diverse mixtures of crops (Mundt, 2002). This association between low diversity and high disease incidence is called the ‘monoculture effect’ (for example, Elton, 1958; Leonard, 1969; Garrett and Mundt, 1999; Zhu *et al.*, 2000; Pilet *et al.*, 2006). Here, we examine how genetic diversity affects the spread of disease in natural populations. We also consider the theoretical basis for the monoculture effect in host populations, and suggest that there may be a ‘diversity threshold’ for disease spread.

PATTERNS OF GENETIC DIVERSITY AND DISEASE SPREAD

The most notable examples of the monoculture effect in natural populations come from the dramatic epidemics in small populations

of endangered species, particularly mammals (for example, O’Brien *et al.*, 1985; Thorne and Williams, 1988). Genetic bottlenecks have reduced the genetic variability in cheetahs, particularly at the major histocompatibility complex, and endangered populations of these animals have been decimated by coronavirus epizootics (O’Brien *et al.*, 1985). Similarly, the endangered black-footed ferret may have been extirpated from its natural habitat, because low genetic diversity aided the spread of a virulent canine distemper epizootic (Thorne and Williams, 1988).

Range expansion and habitat isolation caused by human activities can also generate small, founder populations with low genetic diversity. Newly-colonised, western populations of Italian agile frogs (*Rana latastei*) are genetically depauperate, and they have an increased susceptibility to a novel, emerging *Ranavirus* (Pearman and Garner, 2005). Similarly, dam construction in the Senegal river basin likely permitted the rapid expansion of snails (*Biomphalaria pfeifferi*), which serve as the first-intermediate host for the human disease schistosomiasis (Campbell *et al.*, 2010). Recently established *Biomphalaria* snail populations are genetically homogenous compared with those in natural habitats in Zimbabwe; they are also more susceptible to infection and this increases the opportunity for parasite transmission to humans (Campbell *et al.*, 2010).

By reducing individual-level and population-level genetic heterozygosity, inbreeding can increase host susceptibility to infectious parasites (Dwyer *et al.*, 1997; Acevedo-Whitehouse *et al.*, 2003; Spielman *et al.*, 2004; Ellison *et al.*, 2011). In wild populations, Acevedo-Whitehouse *et al.* (2003) found that heavily inbred California sea lions were more infected, and consequently, may act as pathogen reservoirs, spreading parasites in sea lion populations. But, is increased susceptibility directly due to reduced diversity, or does inbreeding depression have an effect by compromising host condition? By manipulating the levels of inbreeding in *Drosophila melanogaster*, in laboratory experiments Spielman *et al.* (2004)

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confirmed that the increase in disease susceptibility resulted from a lower frequency of resistance alleles in the population, and not by generalized inbreeding effects. Inbreeding effects were similarly excluded as a reason for why offspring from inbred populations of *Daphnia*, a freshwater crustacean, were more susceptible to a vertically-transmitted parasite than those from outbred populations (Ebert *et al.*, 2007). Finally, Kerstes and Wagner (2012) found that inbreeding increased parasite-induced mortality in the red flour beetle (*Tribolium castaneum*) by prolonging development time, but it did not increase susceptibility to infection.

Founder populations provide the opportunity to examine the effects of inbreeding and small population size on the link between genetic diversity and parasite resistance. For example, in a comparison of founder versus ancestral mainland populations of deer mice, Meagher (1999) found that inbred, island populations in Lake Michigan had higher infection levels and lower genetic diversity. The link between diversity and parasite spread has even been revealed when comparing large and small founder populations. Hawks colonizing smaller Galápagos Islands possessed lower genetic diversity, produced low antibody titer, and had a higher abundance of parasites than more outbred populations on larger islands (Whiteman *et al.*, 2006).

Uniparental forms of reproduction, such as self-fertilization or parthenogenesis, should have similar consequences for parasite resistance as biparental inbreeding. Along these lines, self-fertilizing populations and inbred sexual populations were both found to have higher infection rates by a trematode parasite compared with outbred sexual populations of topminnows (*Poeciliopsis monacha*) (Lively *et al.*, 1990). In another species of partially-selfing fish (*Kryptolebias marmoratus*), Ellison *et al.* (2011) found that outcrossing increased the genetic diversity of wild populations and decreased their susceptibility to multiple parasites.

Mating systems can also directly affect genetic diversity and parasite resistance (Busch *et al.*, 2004; Williams *et al.*, 2011). For example, in eusocial insect colonies, queens can mate with a single male or with multiple males (polyandry), which determines the level of relatedness among individuals within a colony. High relatedness among individuals in a population can enhance the evolution of cooperation (Hamilton, 1964a, b, 1987), but the genetic similarity between individuals may also facilitate the spread of parasites (Shykoff and Schmid-Hempel, 1991; Schmid-Hempel, 1998). As such, multiple mating has been suggested as an evolutionary response to parasite pressure (Hamilton, 1987; Sherman *et al.*, 1988), which may counteract the high risk of parasite transmission and increase the overall productivity of the colony (Schmid-Hempel, 1994; Schmid-Hempel and Crozier, 1999; Brown and Schmid-Hempel, 2003).

Numerous studies on ants and bees have indeed found that multiply mated queens form more resistant colonies (Baer and Schmid-Hempel, 1999, 2001; Tarpay, 2003; Hughes and Boomsma, 2004; Tarpay and Seeley, 2006; Seeley and Tarpay, 2007), and that offspring fathered by different males do vary in susceptibility to infection (Baer and Schmid-Hempel, 2003). Ultimately, the balance between the costs (for example, within-colony conflict, reduced offspring output) and benefits (for example, resistance to a range of parasites) associated with heterogeneity in colonies may determine the optimal level of polyandry (Baer and Schmid-Hempel, 2001; Van Baalen and Beekman, 2006). Polygyny (the presence of multiple queens within a single colony) can also decrease the relatedness among individuals and increase the variety of resistance alleles in the colony. Studies in which the number of founding queens was experimentally manipulated have confirmed that colonies founded

by multiple queens have lower parasite loads (Liersch and Schmid-Hempel, 1998; Reber *et al.*, 2008). In addition, workers from polygynous colonies of an ant (*Cardiocondyla obscurior*) were better at detecting disease and removing infected individuals from the nest than workers from nests having a single queen (Ugelvig *et al.*, 2010).

Increases in infection prevalence in the wild is associated with genetic bottlenecks and inbreeding, induced by founder effects or mating systems. Thus, host population genetic diversity seems to have an important role in buffering populations against epidemics. But, how exactly does genetic diversity reduce disease spread?

HOW MUCH DIVERSITY IS NECESSARY?

An association between genetic diversity and disease spread might be detected by categorizing populations as being either genetically homogenous or diverse. This comparative method can tell us that diversity matters, but does not indicate the amount of genetic diversity required for a population to be resistant, or the 'diversity threshold'. Recently, two insightful empirical studies have quantified the effect of genetic diversity on resistance in host populations. Altermatt and Ebert (2008) and Ganz and Ebert (2010) conducted semi-natural mesocosm and lab experiments, respectively, whereby monoclonal and polyclonal *Daphnia* populations were exposed to microparasites. Parasites spread significantly faster (Altermatt and Ebert, 2008) and infection rates are higher (Ganz and Ebert, 2010) in host monocultures compared with 'polycultures' of several genotypes with higher allelic diversity. These studies suggest that the relationship between host diversity and infection may not be complex, and that a 'handful' of host genotypes in the population can be enough to hamper parasite transmission.

The benefits of host genetic diversity, however, may also depend on the genetic diversity of the parasite population (Boomsma and Ratnieks, 1996; Van Baalen and Beekman, 2006; Ganz and Ebert, 2010). If the parasite population is genetically homogenous, increases in host population genetic diversity might boost the opportunity for parasites to encounter a susceptible host (Boomsma and Ratnieks, 1996; Van Baalen and Beekman, 2006). Alternatively, in a diverse parasite population, there is a high probability that one of a diverse set of parasite genotypes can infect a homogeneous host population (Van Baalen and Beekman, 2006) and genetically diverse host populations are at an advantage. Consistent with these ideas, Ganz and Ebert (2010) found no difference in infection levels among experimental *Daphnia* monocultures and polycultures when populations were exposed to a single-parasite genotype; however, polycultures were more resistant when populations were exposed to multiple parasite genotypes.

THEORETICAL CONSIDERATIONS

There has been surprisingly little theoretical work on the effect of genetic diversity on disease spread. Two models suggest that genetic variation in host susceptibility would not affect infectious disease spread (Springbett *et al.*, 2003; Yates *et al.*, 2006), but it might reduce the severity of infection (Springbett *et al.*, 2003). In these models, hosts varied in susceptibility to a single pathogen strain, but no host genotype was completely resistant to infection. In contrast, Lively (2010a) found that host genetic diversity could reduce the risk of disease spread, assuming that each host genotype was susceptible to a different parasite genotype. This assumption is consistent with the 'matching-alleles' model for infection (Frank, 1993; Otto and Michalakis, 1998). The matching-alleles model is a useful framework for studying self/non-self-recognition systems in animals, and it is supported by studies on invertebrate immunity (Grosberg and Hart, 2000; Carius *et al.*, 2001;

Dybdahl *et al.*, 2008; Duneau *et al.*, 2011; Luijckx *et al.*, 2011). In addition, the framework seems robust to the assumption of single-genotype specificity (Agrawal and Lively, 2002; Engelstaedter and Bonhoeffer, 2009).

The more recent model suggests that increases in the genetic diversity of host populations could have a large effect on disease spread and prevalence at equilibrium (Lively, 2010a). The model assumes that there are no co-infections, and that each parasite genotype can only infect one genetically determined resistance phenotype in the host population, which is the standard assumption of the matching-alleles model for infection. The results suggest that R_0 for each parasite genotype i depends on total host density, as well as the frequency of the matching host genotype, where matches between host and parasite genotypes yield an infection. Thus, disease transmission is both density and frequency dependent. The effect of host density on R_0 is asymptotic on Bg_i , where g_i is the frequency of the matching host genotype, and B is the number of parasite propagules produced by each infection that make contact with a host (Lively, 2010a). Thus, B is equal to the total number of propagules produced by an infection multiplied by the frequency of propagules that contact a host. For large host populations ($N > 200$) the effect of further increasing the host population size has little effect; but, increasing the number of host genotypes has a large effect, because increasing the number of host genotypes decreases the frequency (g_i) of each genotype. Under parasite-mediated, frequency-dependent selection, the frequency of each host genotype would be expected on average to be approximately $1/G$, where G is the total number of host genotypes in the population. Under these conditions, R_0 for large populations is approximately B/G . This result suggests that experimentally doubling the number of host genotypes in the population would reduce R_0 by one half, and that this would be roughly true even if the experiment increased the total number of hosts in the population (assuming the population is already large). The analytical results also suggest that the parasite would die out, following the addition of genetic diversity to the host population, provided that the frequency of each host genotype declines to less than $1/B$.

We used computer simulations to examine the gist of these ideas. The simulations assumed a haploid host with two loci coding for resistance. Each locus could have up to three alleles for a total of nine different genotypes. Each of the host genotypes could be infected by one of nine different parasite genotypes, consistent with the matching-alleles model for infection. In these simulations, birth rates of the host were density dependent, and infection reduced the intrinsic birth rate by 30% (the parameters were chosen for illustrative purposes). The details of the simulation are given in Lively (2010b).

We began the simulation with two alleles at one locus and three alleles at the other locus, giving six possible host genotypes. An uninfected host population was initiated at carrying capacity ($K = 40\,000$), where the number of hosts of each genotype was determined by randomly assigning allele frequencies at the two loci. At generation 1, one host of each genotype was introduced as infected. Thereafter, the infected hosts of each genotype were introduced into the population with a probability of 0.02 per generation, to simulate immigration of infected individuals. We started by assuming $B = 9$, meaning each infection produced nine propagules that contacted a host. From the analytical results we would expect under that the average value for R_0 would be $B/G = 9/6 = 1.5$ (where G is the number of genotypes). As such, the pathogen would be expected to spread in the population, as was indeed the case (Figure 1a). After an initial oscillatory period, the gene frequency

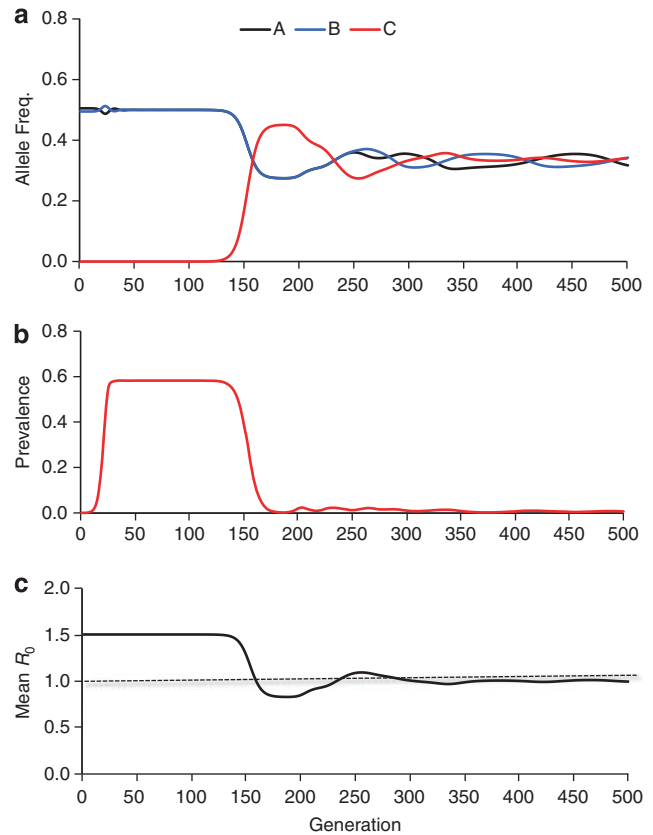


Figure 1 The effect of increasing host genetic diversity on R_0 and the prevalence of infection. A new allele was introduced at generation 100, which increased the number of possible haploid genotypes from six to nine. The simulation is based on the calculations in Lively (2010a); parameter values used were: $a_i = a_u = 0.0001$; $b_u = 10$; $b_i = 7$. As such, virulence was density independent and equal to $0.30 (= 1 - b_i/b_u)$, the parameter values are chosen only for the purpose of illustration of the main ideas. (a) Allele frequencies at the second locus, overtime, in which the new allele C was introduced at generation 100. Note the rapid spread of the newly introduced allele. (b) Prevalence of infection overtime. Note the dramatic decrease in infection prevalence following the spread of the new allele, C. (c) R_0 overtime. Note the rapid decrease in R_0 after the introduction of the new allele, C, at the second locus at generation 100. The dashed line denotes $R_0 = 1$ (epidemiological threshold). Taken together, the results suggest that increasing genetic diversity by the introduction of a single novel allele in the host population can eliminate infection in tens of generations.

dynamics stabilized (Figure 1a), and the prevalence of infection also stabilized for the parameter values considered here (Figure 1b). R_0 converged to the predicted value of 1.5 (Figure 1c).

We then introduced a third allele at the second locus at generation 100, which increased the number of possible genotypes from six to nine. The allele quickly spread, as it conferred resistance on three of the nine possible genotypes for which there was no matching parasite genotype (Figure 1a). Average R_0 quickly dropped to below 1 as the allele spread in the population (Figure 1c), and the frequency of infection declined sharply (Figure 1b). Matching parasite genotypes were introduced into the population by migration (at a rate of 0.02 per genotype per generation), which lead to selection against the new allele after it became common, as well as to a slight increase in R_0 (Figure 1c). This resulted in sufficient selection to equalize allele frequencies so that the frequency of each genotype approximated $1/G$.

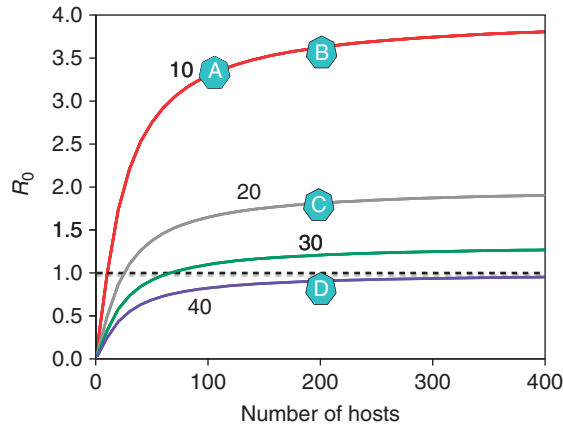


Figure 2 The effect of increasing genetic diversity on R_0 by adding new hosts. Suppose we have 100 hosts, with 10 genotypes in equal frequency (Point A). Now suppose that we experimentally double the host population size, without affecting the genetic diversity (Point B). We see an increase in R_0 , but the increase is not large. Now suppose we double the host population size, but also increase the number of genotypes from 10 to 20 (Point C). We now see a large decrease in R_0 , but it does not go below 1, so the disease can still spread. Finally, suppose that we experimentally double the host population size, but we also increase the number of genotypes by fourfold (Point D). Now R_0 not only decreases, but it goes below 1, so the disease will die out. Redrawn from Lively (2010a).

At this point, R_0 was equal to one ($B/G = 9/9 = 1$), and parasite prevalence fell close to zero, but was maintained at a low level by immigration (Figure 1b).

The point is that introducing a single novel allele in the host population increased the number of possible genotypes by 50%. This led to virtual elimination of the parasite, as the prevalence of infection plummeted from about 60% to near zero. A reduction in prevalence occurred despite the fact that matching parasite genotypes were also introduced into the population, and that the host population size remained large (that is, close to 40 000 individuals; results not shown). Clearly, under the assumptions of the present model, small increases in allelic diversity can cause dramatic reductions in parasitism, even in very large host populations. In addition, elimination of the pathogen is not necessarily followed by a loss of genetic diversity in the host population, as the different host genotypes are selectively neutral in the absence of parasite pressure (Figure 1a).

The available data and the model are consistent with the idea that genetic diversity in host populations can reduce the spread of disease. However, a practical question arises: would the beneficial effect of adding hosts with novel genotypes, in order to increase local genetic diversity, outweigh the positive effect of increasing population size on R_0 ? A possible answer is also suggested by the model, which suggests that the effect of increasing population size on R_0 shows diminishing returns with host density, such that R_0 is asymptotic on B/G (Figure 2). As such, while increasing host population size does strongly affect R_0 in small host populations, it has a small effect in large host populations (Figure 2). This suggests that increasing genetic diversity can still reduce parasite prevalence, even though host population size is also increased. The results in Figure 2 suggest that boosting genetic diversity could overcome the effect of increasing host population size, even when the latter is increased by fourfold.

Critically, the diversity threshold does not work by simply reducing the population size of the individual genotypes. The threshold, in fact,

was calculated by assuming an infinite host population size. Rather it works by reducing the probability of successful infection by reducing the frequency of matching host genotypes for each parasite genotype.

FUTURE DIRECTIONS AND CONCLUSION

Consistent with results from agricultural populations, the existing literature suggests that high genetic diversity could buffer host populations against disease spread. Although observational studies from natural populations of vertebrates (for example, cheetahs, sea lions, fish and frogs) may have limitations, they strongly suggest that diversity matters, and their results are consistent with experimental studies on freshwater crustaceans and social insects. However, several questions remain:

- (1) Does a diversity threshold exist? In other words, can parasites be eliminated by increasing host genetic diversity above some threshold value?
- (2) What are the relative effects of host density and host genetic diversity on disease spread?
- (3) What are the effects of genetic diversity in the parasite population versus that of the host population?
- (4) What is the heritability of parasite resistance in natural populations? Very little is known about the heritability for resistance in natural populations. It should be high in populations where genetic diversity is maintained by parasite-mediated frequency-dependent selection.

These issues would be best addressed by data from natural populations. If parasites take hold or die out depending on how much host genetic diversity exists relative to the threshold, determining whether diversity thresholds exist in natural populations may have great value. This may be particularly helpful for conserving endangered species and mediating vector–human–parasite transmission.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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