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Evolution of pathogen virulence: the role of variation in host phenotype

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Selection on pathogens tends to favour the evolution of growth and reproductive rates and a concomitant level of virulence (damage done to the host) that maximizes pathogen fitness. Yet, because hosts often pose varying selective environments to pathogens, one level of virulence may not be appropriate for all host types. Indeed, if a level of virulence confers high fitness to the pathogen in one host phenotype but low fitness in another host phenotype, alternative virulence strategies may be maintained in the pathogen population. Such strategies can occur either as polymorphism, where different strains of pathogen evolve specialized virulence strategies in different host phenotypes or as polyphenism, where pathogens facultatively express alternative virulence strategies depending on host phenotype. Polymorphism potentially leads to specialist pathogens capable of infecting a limited range of host phenotypes, whereas polyphenism potentially leads to generalist pathogens capable of infecting a wider range of hosts. Evaluating how variation among hosts affects virulence evolution can provide insight into pathogen diversity and is critical in determining how host–pathogen interactions affect the phenotypic evolution of both hosts and pathogens.

Keywords: pathogen; virulence; alternative strategies; polymorphism; polyphenism

1. INTRODUCTION

A pathogen's fitness depends in part on the successful transmission of its propagules to new hosts (see Ewald (1983) and Frank (1996) and references therein; Anderson & May 1981; May & Anderson 1983). Pathogens can increase transmission by enhancing their growth or replication rates and increasing propagule production (see the reviews in Ewald (1983), Frank (1996) and Ebert (1998) and references therein). Yet pathogen growth and propagule production can deplete host resources, damage host tissues and lead to host and, therefore, pathogen death. Thus, pathogens face a trade-off between fecundity and longevity (Frank 1996): enhanced exploitation of hosts may lead to greater propagule production and transmission, but it also potentially reduces host and, therefore, pathogen survival (reviewed in Ewald 1983; Bull 1994; Ebert & Herre 1996; Frank 1996; Lipsitch & Moxon 1997; Ebert 1998; Poulin 1998; e.g. Mackinnon & Read 1999). Natural selection is expected to favour pathogens that maximize their fitness by expressing growth, reproductive rates and a concomitant level of virulence (the damage done to the host by the pathogen) that optimizes this trade-off (Anderson & May 1981; Levin & Pimentel 1981; Bremermann & Pickering 1983; Ewald 1983; May & Anderson 1983; Frank 1996).

A further problem faced by pathogens is that host populations can consist of individuals that pose different selective environments to pathogens (Schmid-Hempel & Koella 1994). Consequently, the level of virulence that maximizes pathogen fitness in one host may be selected against in an alternative host such that one level of virulence may not be appropriate for all host types. Here, I review how hosts can vary in the selective factors affecting pathogen fitness and consider how this variation affects the evolution of virulence. My use of virulence throughout this paper refers to the damage done to hosts that is caused by pathogen growth or replication and propagule production.

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2. HOST PHENOTYPE AND VARYING SELECTION ON PATHOGENS

Generally, several selective factors affect the level of virulence favoured for a given host phenotype. These factors are risk of host mortality, host immune response to pathogen infection, opportunities for pathogen transmission and the kinship or competitive environments faced by the pathogen within the host. These factors are listed in table 1 along with their predicted evolutionary effects on pathogen phenotype. As I discuss below, variation in host phenotype can potentially cause each factor to vary among hosts, creating different selective environments among different hosts.

One way in which hosts vary is in their likelihood of mortality. For example, different age classes, sexes, genotypes and phenotypic morphs (such as insect castes) may exhibit differential mortality that is caused by the damage associated with a given level of growth and reproduction by the pathogen (for examples, see Roberts *et al.* 1995; Imhoof & Schmid-Hempel 1998; Nolan *et al.* 1998). Pathogens may also cause differential mortality among hosts if infection makes certain hosts more susceptible to predation, starvation or additional infection by other pathogens (Schmid-Hempel 1998). Because hosts can be differentially susceptible to the effects of pathogen infection, pathogens expressing rapid growth and propagule production may kill vulnerable hosts before the maximum number of propagules are transmitted. Yet, pathogens expressing reduced growth and reproduction in hosts that could withstand higher levels would forgo reproductive opportunities.

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Table 1. *Factors affecting the evolution of growth or replication rates, propagule production and concomitant level of virulence expressed by pathogens*

(See also the citations in each of the references listed in the last column.)

selective factor	predicted response by pathogen	references
pathogen-induced host mortality	reduce growth or replication and propagule production in order to extend host longevity	Levin & Pimentel (1981), Ewald (1983), Frank (1996) and Poulin (1998)
externally induced host mortality	increase growth or replication and propagule production in order to maximize fitness before host death	Poulin (1998) and Schmid-Hempel (1998)
host immune response	increase growth or replication and propagule production in order to swamp host defences and maximize fitness before clearance from host	Antia *et al.* (1994), Frank (1996), Antia & Lipsitch (1997) and Lipsitch & Moxon (1997)
opportunities for transmission and/or new infections	greater opportunities lead to enhanced growth or replication and propagule production in order to take advantage of reproductive opportunities; fewer opportunities lead to reduced growth or replication and propagule production in order to preserve the host and maximize chances for future reproductive opportunities	Ewald (1983), Bull *et al.* (1991), Herre (1993), Clayton & Tompkins (1994), Lenski & May (1994), Lipsitch & Nowak (1995), Lipsitch *et al.* (1995), Ebert & Herre (1996), Combes (1997), Poulin (1998) and Schmid-Hempel (1998); but see Lipsitch & Nowak (1995) and Lipsitch *et al.* (1996)
competitive or kinship environment	competition with unrelated strains within the host selects for rapid growth or replication, propagule production and use of host resources; kinship among pathogens selects for reduced growth or replication and use of host resources via kin selection	Bremermann & Pickering (1983), Ewald (1983), Frank (1992, 1994, 1996), Nowak & May (1994) and Taylor *et al.* (1998)

Hosts may also exhibit differential mortality due to factors other than pathogen infection. For instance, social insect workers may have higher mortality than other castes (reviewed in Schmid-Hempel 1998), dispersers may have higher mortality than residents (e.g. Daniels & Walters 2000) and mortality may vary with sex, size or reproductive behaviour (e.g. Tatar *et al.* 1993; Alcock 1996; Torres & Drummond 1997; Gotthard *et al.* 2000). Host mortality due to extrinsic factors favours enhanced pathogen virulence in order to maximize reproduction before host death (table 1). Thus, pathogens that are successful by expressing reduced virulence in those host phenotypes with low mortality may be less successful in hosts with high mortality because opportunities for reproduction will be curtailed by host death.

Host immune responses can also vary among hosts (e.g. between sexes or age classes) (Weksler 1994; Roberts *et al.* 1995; Walker *et al.* 1997; Bernstein & Murasko 1998; Gaillard & Spinedi 1998; Rosen *et al.* 1999) so that pathogens face different within-host selective environments among alternative host phenotypes. For example, in some species males, as opposed to females, suffer immune system suppression during the breeding season when males invest energy in sexual display rather than immune system function (Westneat & Birkhead 1998; e.g. Gonzalez *et al.* 1999; Verhulst *et al.* 1999). Such variation selects for different levels of virulence in alternative hosts. Whereas hosts with effective immune responses favour enhanced virulence in order to maximize fitness prior to clearance, hosts with less effective immune responses favour reduced virulence in order to extend host longevity (table 1).

Opportunities for propagule transmission can also vary among hosts. For example, some hosts may be avoided when infected (Loehle 1995) whereas other hosts may not be avoided. To illustrate this possibility, consider a situation where males display in order to attract mates and females are the selective sex (for examples see Andersson 1994). By inspecting males, females avoid males that suffer pathogen infection (e.g. Clayton 1990; Zuk *et al.* 1990; Buchholz 1995). Thus, pathogens that require social contact for transmission may be under selection in males to 'conceal' themselves by reducing virulence (table 1) (Combes 1997; Knell 1999). Conversely, if females generally mate successfully, regardless of infection status, higher levels of virulence might be favoured in females because of enhanced transmission opportunities (table 1). Thus, the optimal level of virulence may be lower in males than in females.

Finally, the competitive or kinship environments that pathogens face may vary among different host phenotypes. For instance, many host populations consist of individuals that disperse or forage while others remain resident in a local group (see Schmid-Hempel (1998) for examples in social insects). Pathogens in dispersing hosts may more probably face competitive interactions with unrelated pathogens as the host is subsequently infected by novel pathogen genotypes. Such competition leads to within-host selection for virulent pathogen strains that are best able to use host resources (table 1). In contrast, pathogens in hosts that are resident may more probably occur in kin groups, thereby facing a within-host selective environment that favours reduced virulence through kin selection (table 1).

As discussed above, hosts potentially vary in the factors affecting virulence evolution. Moreover, these selective factors interact with one another and such interactions probably vary among hosts. Thus, a level of virulence

that maximizes pathogen fitness in one host phenotype may lead to low fitness in another host phenotype. How then does variation in selection on pathogens among hosts affect virulence evolution? I address this question below.

3. EVOLUTION OF ALTERNATIVE VIRULENCE STRATEGIES

Theoretical models generally predict four alternatives by which organisms can adapt to varying selective environments (Levins 1968; reviewed in Schlichting & Pigliucci 1998). Each alternative can apply to host–pathogen systems.

First, selection might favour the expression of a single level of virulence across all host phenotypes. If hosts reveal fine-scale variation or if a single optimal level of host exploitation exists for all host environments, then a single level of virulence may evolve (*sensu* Levins 1968; see also Schlichting & Pigliucci 1998). However, note that in the former case, selection may favour a level of virulence that is a good solution across all host phenotypes, but which may not be optimal for any particular host phenotype (Ebert & Hamilton 1996; Antia & Lipsitch 1997).

Second, selection may favour facultative expression of virulence that varies continuously with the host environment if optimal virulence is a continuous function of host phenotype and if pathogens can assess their environment (Frank 1992; Imhoof & Schmid-Hempel 1998; Taylor *et al.* 1998; see also Levins 1968; Schlichting & Pigliucci 1998). For example, increasingly stronger immune systems may favour increasing virulence. If pathogens detect immune system strength (e.g. via biochemical cues), they could 'acclimate' to the host environment by expressing an appropriate level of virulence. A possible example of this may occur in the freshwater snail (*Potamopyrgus antipodarum*) that is infected by a *Microphallus* trematode. When the hosts are in poor condition, as opposed to good condition, the parasite seemingly reduces its level of virulence in order to enhance the likelihood of transmission to its ultimate host (Jokela *et al.* 1999).

In the two situations above, the pathogen potentially has high fitness across the range of host variation. If, however, a given level of virulence confers high fitness in certain host phenotypes but low fitness in alternative host phenotypes, then selection may maintain alternative virulence strategies in the pathogen population (*sensu* Levins 1968; Moran 1992; see also Schlichting & Pigliucci 1998). Alternative virulence strategies may exist as a genetically encoded polymorphism (e.g. Bonhoeffer & Nowak 1994; Nowak & May 1994; May & Nowak 1995; Regoes *et al.* 2000) or they may be facultatively expressed by individual pathogens (Frank 1992; Imhoof & Schmid-Hempel 1998; Taylor *et al.* 1998). I discuss these possibilities below.

If pathogens consistently infect the same host phenotype, selection may favour specialized pathogen strains that are adapted to the host phenotype they often infect (see Ebert & Hamilton (1996) and references therein; Lively & Dybdahl 2000) and evolutionary maintenance of alternative (polymorphic) virulence strategies. Regoes *et al.* (2000) examined how virulence evolves when pathogens cannot express the same level of virulence in alternative host types. They found that specialization on alternative host types depends on the cost of switching from one host to another. Higher costs of switching hosts lead to greater specialization, whereas lower costs lead to pathogen strains that express an intermediate level of virulence across all host types (Regoes *et al.* 2000). These results suggest that the evolution of a single virulence strategy versus alternative virulence strategies depends on the strength of the trade-off in fitness among alternative host phenotypes (see also Levins 1968; Castillo-Chavez *et al.* 1997). Although polymorphic virulence strategies can occur for reasons other than as adaptations to varying selective environments among hosts (e.g. Bonhoeffer & Nowak 1994; Nowak & May 1994; Gupta & Hill 1995), trade-offs in fitness among different host environments are a potentially important but largely unexamined explanation for the evolution of polymorphic virulence.

If pathogen strains specialize on particular hosts, it is critical to the pathogen's success that its propagules are transmitted to hosts for which it is adapted. Such transmission may occur, for example, if particular host types tend to interact with one another rather than with alternative host types or if pathogens actively settle on the appropriate host. Indeed, pathogens may manipulate host behaviour in order to ensure infection of the appropriate host phenotype (reviewed in Poulin 1998).

Contrary to situations where pathogens transmit propagules among the same host phenotypes, propagule transmission may occur among different host phenotypes. Consequently, the host environment that a pathogen experiences may be relatively unpredictable. If infection of different host phenotypes tends to be equally likely, then selection may favour facultative expression of the virulence strategy (polyphenism) (*sensu* Levins 1968; Moran 1992; see also West-Eberhard 1989; Schlichting & Pigliucci 1998) selectively favoured in the host the pathogen infects (Frank 1992; Imhoof & Schmid-Hempel 1998; Taylor *et al.* 1998). Evolution of facultatively expressed virulence strategies requires that pathogens assess their environment reliably (*sensu* West-Eberhard 1989; Moran 1992), which is possible given that hosts can vary perceptibly. For example, pathogens may use biochemical cues associated with immune responses or differences in the type or amount of circulating hormones in order to evaluate the host environment (Taylor *et al.* 1998).

The evolution of polymorphic versus polyphenic virulence has important implications for host–pathogen coevolution. If pathogens become increasingly specialized for infection of particular hosts (polymorphism), the pathogens' ability to infect other host types or even other host species successfully may become limited (e.g. Lively 1989; Ballabeni & Ward 1993; Ebert 1994, 1998; Ebert *et al.* 1998; reviewed in Thompson 1994; Poulin 1998). Moreover, if the host population undergoes speciation associated with phenotypic differences, then the pathogen population may also undergo speciation, leading to diversification of pathogen fauna corresponding to the diversification of hosts (reviewed in Poulin 1998). In contrast, the evolution of polyphenic virulence may lead to generalist pathogens. Indeed, those pathogens that facultatively express virulence may successfully infect not only various host phenotypes of a single species, but also hosts of different species. Thus, how hosts differ and how different

hosts interact may be important for the evolution of generalist versus specialist pathogens.

4. CONCLUSION

Few studies have explicitly evaluated whether pathogens facultatively alter their virulence in order to maximize fitness in any given host environment (e.g. Imhoof & Schmid-Hempel 1998; Taylor *et al*. 1998). Thus, whether pathogens facultatively adopt alternative virulence strategies in order to maximize fitness remains unclear. A larger body of work exists to suggest that many pathogen populations may be polymorphic for virulence expression (e.g. Gupta *et al*. 1994; Ebert *et al*. 1998; Grassly *et al*. 1998). For example, serial passage experiments have illustrated that some pathogens readily evolve specialization for the hosts they commonly infect (reviewed in Ebert 1998). Yet, whether virulence polymorphisms are commonly maintained as adaptive strategies for varying selective environments among different hosts remains unknown.

The evolution of polymorphic virulence may be more common in microparasites that can evolve rapidly within the host. Indeed, microparasitic species have a number of genetic mechanisms that generate diversity and allow for adaptation to a particular host environment (reviewed in Moxon 1999; Read *et al*. 1999). In contrast, polyphenic virulence may be more common among macroparasites that do not evolve within the host. For these pathogens, facultative expression of alternative virulence strategies may be the most effective means of adapting to novel or varying host environments.

Evaluating the above predictions requires assessing how selection varies among hosts and determining whether pathogens respond to this variation in a way that maximizes fitness. In doing so, however, two factors must be considered. First, whether or not the host–pathogen system is at equilibrium can alter the importance of selective factors impinging on pathogens and change the nature of virulence evolution (e.g. Bremermann & Pickering 1983; Lipsitch & Nowak 1995; Bonhoeffer *et al*. 1996). Consequently, testing these predictions in both equilibrium and non-equilibrium situations is necessary for understanding the evolution of virulence in any given host–pathogen system. Second, host response to infection (e.g. disease symptoms) can be confounded with variation in the virulence strategy expressed by the pathogen (Poulin 1998; Taylor *et al*. 1998; Poulin & Combes 1999). Thus, measurements of virulence should not rely strictly on host response to the pathogen (e.g. mortality rates) (Poulin 1998; Taylor *et al*. 1998; Poulin & Combes 1999). Instead, measures of pathogen growth or replication rates and transmission rates should be combined with measures of damage to the host in order to describe pathogen virulence strategies better (Taylor *et al*. 1998).

The complex relationship between pathogens and their hosts is only beginning to be understood. Heterogeneity in host phenotype potentially shapes the evolution of pathogen infection strategies in profound ways. Pathogen infection strategies may in turn alter the expression, variation and evolution of host phenotypes (Minchella 1985; Hochberg *et al*. 1992; Shykoff & Schmid-Hempel 1991; Shykoff & Kaltz 1998). Addressing these issues will provide a better understanding of pathogen evolution and its consequences for the evolution of host phenotypes.

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