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Epidemiological and evolutionary consequences of life-history trade-offs in pathogens

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Trade-offs in life-history traits are a central tenet in evolutionary biology, yet their ubiquity and relevance to realized fitness of populations remains questioned. Trade-offs in pathogens are of particular interest because they may constrain the evolution and epidemiology of diseases. Here, studies that have measured life-history trade-offs in pathogens (fungi, oomycetes and viruses) of agricultural crops, as well as pathogens attacking wild host plants, are reviewed. The majority of studies report a penalty associated with high virulence as is evidenced by lower performance during subsequent life-history stages. However, costs are not pervasive, and the strength and even shape of life-history correlations can vary according to host genotype, and abiotic environment. Importantly, life-history trade-offs are shown to have profound epidemiological implications ranging from lower disease prevalence of strains harbouring unnecessary virulence, to increased extinction risk at the metapopulation level. From an evolutionary perspective, costs of virulence are shown to constrain the range of *R* genes, and hence host genotypes, a given strain can adapt to. Moreover, costs of virulence play an important role in limiting the host range of pathogens. Hence, analysis of pathogen life history plays a key role in identifying means of battling disease, from breeding durable resistance to epidemiological intervention strategies.

Keywords: aggressiveness, cost of virulence, fitness, gene-for-gene, infectivity, plant–pathogen interactions

Introduction

Variation in pathogen fitness is ubiquitous across multiple spatial and temporal scales (Tack *et al.*, 2012). The observed variation in key traits that underlie host–pathogen interactions is puzzling. For pathogens, the ability to infect hosts is the prerequisite of their survival and reproduction, and hence, high virulence should always be favoured. Yet, pathogen populations typically contain strains that are inferior in their pathogenicity traits compared to other co-occurring strains (Tack *et al.*, 2012). Genetic variation in patterns of host susceptibility and pathogen virulence and aggressiveness are essential underlying factors influencing disease epidemiology (Wolfe, 1985; Garrett & Mundt, 1999; Mundt, 2002; Laine, 2004) and the emergence and spread of new diseases (Parker & Gilbert, 2004; Friesen *et al.*, 2006; Fisher *et al.*, 2012). Hence, understanding what processes maintain diversity in host–pathogen interactions is at the heart of finding sustainable means of battling disease.

The current understanding of the maintenance of variation in resistance and pathogenicity is largely based on theoretical predictions. Antagonistic co-evolution between hosts and pathogens has been invoked as a key driver of biological diversity (Bergelson *et al.*, 2001; Tian *et al.*, 2003). The gene-for-gene (GFG) framework has been proposed as the genetic mechanism by which hosts and pathogens interact. According to the GFG model, each corresponding host resistance (*R*) gene interacts specifically with an avirulence (*AVR*) gene in the pathogen to determine infection outcome (Flor, 1956). An elicitor carried by an *AVR*-pathogen is recognized by the host *R*-allele product, triggering local and systemic defence responses in the host (Dangl & Jones, 2001). Plants that lack the *R* gene are susceptible (*r*), and pathogens with a modified *AVR* factor are virulent (*avr*). A key characteristic of the GFG mechanism is universal virulence of the *avr*-allele because it is capable of infecting both *R* and *r* host genotypes. The GFG hypothesis stimulated a series of deterministic theoretical models exploring how the frequencies of resistance and virulence genes change over time in host and pathogen populations, respectively (reviewed in Laine & Tellier, 2008). A consistent feature of these models is a high cost associated with virulence (or resistance) that is required to maintain diversity (Laine & Tellier, 2008).

Costs of virulence arise from trade-offs between life-history traits, whereby allocation of limited resources in one trait has a negative impact on another trait, and it is a generally accepted phenomenon in evolutionary biology (Stearns, 1989). The trade-off model provides an intuitive framework for explaining how adaptation of populations to new environments may be constrained, and how different life-history strategies evolve, depending on where limited resources are allocated (Maynard Smith, 1966; Rausher, 1984; Roff, 1992). In GFG interactions, a mutation from avirulence to virulence is always associated with an increase in fitness in the presence of a matching *R* gene, as it enables the pathogen to

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survive and reproduce on a host genotype that was previously unavailable to the pathogen. As virulence often evolves via mutational loss of function of genes that would otherwise elicit a defence reaction of the host (Vera Cruz *et al.*, 2000), this advantage of malfunctioning can turn into a disadvantage if these genes also function during subsequent development of infection (White *et al.*, 2000; Leach *et al.*, 2001; Luderer & Joosten, 2001; Skamnioti & Ridout, 2005). Vanderplank (1968) advocated this mechanism to explain how virulence polymorphism can be maintained in pathogen populations exposed to hosts with *R* genes.

Here, literature on plant–pathogen interactions is reviewed to determine whether there is support for the trade-off hypothesis in plant pathogens. More specifically, this review aims to: (i) describe how fitness costs are measured in plant pathogens; (ii) quantify the types and extent of costs that have been detected in various pathosystems; (iii) assess whether costs are fixed, or whether their expression is mediated by hosts or abiotic environmental conditions; and (iv) examine what the evolutionary and epidemiological consequences of such costs are.

Literature search

Studies from the literature were gathered by browsing the ISI Web of Science database using a combination of search terms such as 'fungus', 'virus', 'plant', 'cost', 'trade-off', 'aggressiveness', 'virulence' or 'infectivity'. Additional studies were collected by screening references of key papers on the same topic, and by checking papers citing these key articles. Reviews and theoretical articles were discarded, resulting in 31 studies that were relevant for the present paper. The following information was extracted from each study: (i) host and pathogen species name, (ii) the measured traits (virulence, aggressiveness, spore production/viral content, size of lesion, latent period, transmission success rate and other traits), and (iii) whether some evidence of trade-off between different pathogen traits was detected in the study. These data are compiled into Table 1. The cost of avirulence genes on fitness of bacterial plant pathogens has been reviewed by Leach *et al.* (2001) and is therefore not included in this study. Overall, 24 pathogen species (and formae speciales) were considered on 19 different plant hosts. Some pathosystems have been studied for different trade-offs, as for example the interaction between *Solanum tuberosum* and *Phytophthora infestans* which has been investigated for the relationship between virulence and a fitness measure accounting for several pathogen life-history traits (Montarry *et al.*, 2010), and for the relationship between overwintering and aggressiveness (Montarry *et al.*, 2007). The same type of trade-off has been investigated for different pathogen species colonizing the same host species. For example, studies of *Puccinia graminis* f. sp. *tritici* (Grant & Archer, 1983), *Puccinia triticina* (Kolmer, 1993) and *Puccinia striiformis* f. sp. *tritici* (Bahri *et al.*, 2009) infecting *Triticum aestivum* provide contrasting results regarding trade-offs.

Defining pathogen traits and trade-offs

To prevent confusion in terminology, the definitions in this review are explicitly spelled out here. Virulence is defined in line with the original GFG framework, whereby virulence is the ability of a pathogen to overcome host resistance; aggressiveness is the extent of damage to the host (often used also to convey transmission capacity; Pariaud *et al.*, 2009). Specific life-history stages describe the extent of within-host growth (e.g. latent period, spore production). Some studies have further constructed fitness measures based on the measured pathogen life-history stages corresponding to the basic reproduction number (R0) in mathematical and evolutionary epidemiology (e.g. Montarry *et al.*, 2010).

Studies that have investigated trade-offs can be divided into two main categories. The first category (14 studies) explores trade-offs between virulence and other fitness traits of the pathogen. The majority of these studies involve fungal species (nine articles), followed by viral pathogens (four studies) and one study concerns an oomycete species. The second category (seven studies) measures the trade-off between pathogen between-host transmission and aggressiveness, although in two studies (Pagán *et al.*, 2007; Agudelo-Romero *et al.*, 2008) the transmission rate is only indirectly estimated by measuring the viral content. Four of these studies investigate this trade-off for viral species, two articles deal with oomycete species and one involves a fungal pathogen.

Measuring fitness costs

The most common method for assessing life-history trade-offs in plant pathogens is through controlled inoculation experiments. Inoculation studies can be divided into two groups: (i) studies that estimate the relative fitness of genotypes with *avr* or *AVR* alleles in experiments under controlled conditions without detailed knowledge of the genetic background (e.g. Thrall & Burdon, 2003), and (ii) studies that compare infection components in near-isogenic pathogen isolates (Bahri *et al.*, 2009; Huang *et al.*, 2010; Montarry *et al.*, 2010) or using strains that have been genetically characterized (Montarry *et al.*, 2010). Control of the genetic background effect can also be fulfilled by using a genome sequencing approach (Desbiez *et al.*, 2003) or by crossing isolates that contrast in their virulence and testing the progeny for fitness costs of unnecessary virulence (Bronson & Ellingboe, 1986; Kolmer, 1993). In addition to inoculation of strains alone, competition experiments have been employed to detect virulence trade-offs (e.g. Bahri *et al.*, 2009).

It is well established that infection development may strongly depend on both host genotype and the abiotic environment (Salvaudon *et al.*, 2008; Wolinska & King, 2009). Hence, whilst there may be evidence for negative correlations within a particular environment, correlations can shift when pathogens encounter different environmental conditions (van Noordwijk & de Jong, 1986; Sgrò & Hoffmann, 2004). Several studies have accounted

Table 1 Summary of studies that investigate the existence of trade-offs in fungal and viral plant pathogens

Reference details	Host species/pathogen species	Measured traits							Evidence of trade-off
		Virulence	Aggressiveness	Spore production / viral content	Size of lesion	Latent period	Transmission success rate	Other traits	
Agudelo-Romero *et al.* (2008)	*Nicotiana tabacum – Capsicum annuum/ Tobaco etch potyvirus*		X	X				Host-specialization experiment	Yes
Bahri *et al.* (2009)	*Triticum aestivum/Puccinia striiformis* f. sp. *tritici*	X						Competition experiment	Yes
Bronson & Ellingboe (1986)	*Triticum aestivum/Blumeria graminis* f. sp. *tritici*	X						Competition experiment/temporal variation of competing strains frequency	No
Carson (1998)	*Zea mays/Cochliobolus heterostrophus*				X			Overwintering success rate	Yes
Desbiez *et al.* (2003)	*Cucurbita pepo/Zucchini yellow mosaic virus*		X	X				Competition experiment	Yes
Doumayrou *et al.* (2013)	*Brassica rapa/Cauliflower mosaic virus*		X				X		Yes
Fraile *et al.* (2011)	*Capsicum annuum/Tobacco mild green mosaic virus – Pepper mild mottle virus*	X						Competition experiment/evolution of avirulence gene/RNA quantification of the pathogen	Yes
Geffroy *et al.* (1999)	*Phaseolus vulgaris/Colletotrichum lindemuthianum*	X						Cross inoculation experiment	Yes
Grant & Archer (1983)	*Triticum aestivum/Puccinia graminis* f. sp. *tritici*	X						Temporal variation of avirulence gene frequency	Yes
	Hordeum vulgare/Blumeria graminis f. sp. *hordei*	X						Temporal variation of avirulence gene frequency	Yes
Héraudet *et al.* (2008)	*Arabidopsis thaliana /Hyaloperonospora parasitica*		X			X	X		Yes
Huang *et al.* (2006)	*Brassica napus/Leptosphaeria maculans*	X			X			Number of lesions/number of lesions producing pycnidia/growth in host tissue/temporal variation of avirulence gene frequency	Yes
Huang *et al.* (2010)	*Brassica napus/Leptosphaeria maculans*	X			X			Number of lesions/incubation period/growth in host tissue/ temporal variation of avirulence gene frequency	Yes
Janzac *et al.* (2010)	*Capsicum annuum/Potato virus Y*	X		X				Competition experiment	Yes
Jenner *et al.* (2002a)	*Brassica napus/Turnip mosaic virus*	X						Competition experiment	Yes
Jenner *et al.* (2002b)	*Brassica napus/Turnip mosaic virus*	X						Competition experiment	Yes
Kolmer (1993)	*Triticum aestivum/Puccinia triticina*	X						Competition experiment	No
Kover & Clay (1998)	*Danthonia compressa/Atkinsonella hypoxylon*		X				X		Yes
Leonard (1969)	*Avena sativa/Puccinia graminis* f. sp. *avenae*	X		X				Competition experiment/number of lesions	Yes

(continued)

Table 1 (continued)

Reference details	Host species/pathogen species	Measured traits							Evidence of trade-off
		Virulence	Aggressiveness	Spore production / viral content	Size of lesion	Latent period	Transmission success rate	Other traits	
Montarry *et al.* (2007)	*Solanum tuberosum/Phytophthora infestans*			X	X	X		Overwintering success rate	No
Montarry *et al.* (2010)	*Solanum tuberosum/Phytophthora infestans*	X		X		X		Lesion growth rate	Yes
Montarry *et al.* (2012)	*Capsicum annuum/Potato virus Y*		X	X			X		No
Pagán *et al.* (2007)	*Arabidopsis thaliana/Cucumber mosaic virus*		X					RNA quantification of the pathogen	Yes
Pariaud *et al.* (2013)	*Triticum aestivum/Puccinia triticina*			X		X			Yes
Sacristán *et al.* (2005)	*Cucumis sativus – Phaseolus vulgaris – Lycopersicon esculentum/Cucumber mosaic virus*		X					Host-specialization experiment/ RNA quantification of the pathogen	No
Salvaudon *et al.* (2005)	*Arabidopsis thaliana/Hyaloperonospora parasitica*		X				X		Yes
Salvaudon *et al.* (2007)	*Arabidopsis thaliana/Hyaloperonospora parasitica*		X				X		Yes
Sicard *et al.* (2007)	*Phaseolus vulgaris/Colletotrichum lindemuthianum*	X	X						No
	Phaseolus coccineus/Colletotrichum lindemuthianum	X	X						No
Susi & Laine (2013)	*Plantago lanceolata/Podosphaera plantaginis*	X		X		X			Yes
Thrall & Burdon (2003)	*Linum marginale/Melampsora lini*	X		X					Yes
Toffolatti *et al.* (2012)	*Vitis vinifera/Plasmopara viticola*		X	X				Leaf tissue colonization/DNA quantification of the pathogen	No
Zhan *et al.* (2002)	*Triticum aestivum/Mycosphaerella graminicola*		X					Competition experiment	No

for this by measuring the shape of trade-offs across different host genotypes (Susi & Laine, 2013) and abiotic gradients (Huang *et al.*, 2010). Moreover, monitoring changes in *avr* gene frequencies in field populations of pathogens yields direct evidence for how trade-offs may impact on epidemiological dynamics. Variation in fitness detected in the laboratory does not always reflect the degree of variation expressed under field conditions. Under natural conditions, stress can increase the genetic variance in fitness, whilst controlled laboratory conditions may mask underlying variation (Sgrò & Hoffmann, 2004). For example, in *P. striiformis* f. sp. *tritici*, field assays revealed even stronger fitness differences between the competing isolates than measurements under controlled conditions (Bahri *et al.*, 2009).

Molecular biology provides powerful tools for quantifying pathogen levels in the host (e.g. RNA quantification; Fraile *et al.*, 2011), for controlling for relatedness between strains (Montarry *et al.*, 2010), and for following the relative performance of strains in competition experiments (strain-specific qRT-PCR method; Jenner *et al.*, 2002a). Serological tests have also been used for quantifying viral levels in the infected host (Desbiez *et al.*, 2003).

Fitness costs of virulence under controlled conditions

Many of the studies that measured fitness costs of virulence also found evidence for such costs. In *P. striiformis* f. sp. *tritici*, a pairwise competition experiment of near-isogenic genotypes that differed by a single virulence factor (*vir4*, *vir6* and *vir9*) revealed that two out of three virulence factors imposed substantial fitness costs in the absence of the corresponding resistance genes. The most probable cause of this competitive disadvantage is a reduction in the ability to develop on the host and produce spores and, at least for the *vir9* virulence gene, direct evidence confirms a cost to sporulation (Bahri *et al.*, 2009). In the pepper-infecting tobamoviruses, fitness penalties of virulence were also confirmed experimentally. Multiplication rates in singly infected susceptible hosts were significantly higher for the avirulent isolate (P_0) than for the virulent isolates, and in competition experiments, pathotype P_0 isolates were competitively superior (Fraile *et al.*, 2011). A reduction in spore production of virulent strains has also been detected in *Melampsora lini* infecting wild flax (Thrall & Burdon, 2003).

Fitness costs of virulence have also been documented for a range of other life-history traits. In *Leptosphaeria maculans*, there is a measurable fitness cost for *avrLm1* compared to *AvrLm1* isolates in terms of number of lesions, size of lesions, distance grown through leaf tissue towards the petiole in controlled experiments and systemic growth from leaf lesions to stems in field experiments. It has also been shown in this pathosystem that fitness costs of virulence alleles varied for different *AVR* genes (Huang *et al.*, 2006, 2010). In *P. infestans*, fitness was assessed by combining several life-history traits (latent period, spore density and lesion growth rate) measured on leaflets of the potato cultivar Bintje, which lacks resistance genes. A statistically significant fitness cost was found in isolates virulent to the *R10* resistance gene. Similar trends, although not statistically significant, were observed for the other genes tested (Montarry *et al.*, 2010). A high cost to competitiveness was detected in *Potato virus Y* (PVY) on host plants devoid of *Pvr4* resistance (Janzac *et al.*, 2010).

Fitness costs of other pathogen life-history traits

Whilst costs of virulence are among the most studied, there is also evidence for trade-offs in other life-history stages in plant pathogens (Table 1). In *Zucchini yellow mosaic virus*, the aggressive mutants were more fit than wildtype strains in mixed infections of tolerant zucchini, but they presented a drastic fitness loss in mixed infections of susceptible zucchini or melon. Thus, aggressive variants may be selected against in susceptible crops (Desbiez *et al.*, 2003). In PVY, adaptation to quantitative resistance was associated with a fitness cost (virus concentration) on the susceptible cultivar, but had no effect on aggressiveness, which could be explained by a high tolerance level, or on aphid transmission efficiency (Montarry *et al.*, 2012). Doumayrou *et al.* (2013) confirmed, in accordance with the classical trade-off hypothesis, a positive correlation between transmission and aggressiveness in *Cauliflower mosaic virus*. However, no correlation was found between within-host accumulation of the pathogen and aggressiveness or transmission. This is probably a result of the existence of two groups of strains with very different within-host accumulation profiles. In *P. infestans*, no trade-off was detected between isolate aggressiveness and overwinter survival of infected tubers. This suggests that the relative frequency of aggressive strains should gradually increase in *P. infestans* populations, unless a trade-off occurs at another stage of the life cycle (Montarry *et al.*, 2007).

In *Arabidopsis thaliana*, *Hyaloperonospora parasitica* infections that sporulated more rapidly (short latent period) transmitted spores less well, revealing a phenotypic trade-off between these important life-history traits. This phenotypic trade-off may help explain how variation is maintained in the latent period in nature (Héraudet *et al.*, 2008). A similar genetic trade-off was identified in the interaction between *P. triticina* and wheat (Pariaud *et al.*, 2013). Interestingly, in this pathosystem the relationship between latent period and spore production varies depending on the host genotype. A positive correlation between virus multiplication and aggressiveness was found in the *A. thaliana–Cucumber mosaic virus* interaction for a small number of the accessions analysed (Pagán *et al.*, 2007). This finding supports the classic trade-off hypothesis whereby within-host parasite multiplication has negative consequences on host fitness, and hence aggressiveness is an unavoidable consequence

of parasite growth and reproduction (Anderson & May, 1982). Other studies have not detected this trade-off (Sacristán *et al.*, 2005; Salvaudon *et al.*, 2005).

Condition-dependent fitness costs

Given that disease expression is determined by pathogen genotype, host genotype, the environment and their interaction – as summarized in the disease triangle (Stevens, 1960) – it is not surprising that host genotype and abiotic environment impact on the shape and direction of life-history correlations in pathogens. A number of studies have found that, whilst there may not be evidence of a general trade-off, strong fitness costs of pathogens are detected on some host genotypes (Salvaudon *et al.*, 2005; Pagán *et al.*, 2007; Héraudet *et al.*, 2008; Huang *et al.*, 2010). Hence, there is a need to use a range of plant genotypes to detect pathogen fitness costs that may be rare or even absent on some genotypes (Huang *et al.*, 2010; Pariaud *et al.*, 2013). In the interaction between *Plantago lanceolata* and its powdery mildew, *Podosphaera plantaginis*, Susi & Laine (2013) found that trade-offs are mediated by adaptation to the host. Positive correlations between virulence and subsequent life-history stages were detected on sympatric host plants, but on allopatric hosts these correlations disappeared and even became negative. Together, these results imply that the trade-off hypothesis should not be discarded for any particular pathosystem unless sufficient genetic variation of both the host and the pathogen has been included in the experimental design.

It is well known that temperature is one of the key external determinants of infection development, and that pathogen genotypes may differ in their sensitivity to variation in ambient temperature (Laine, 2007). Huang *et al.* (2010) demonstrated that in *L. maculans* there were differences in the optimal temperature range for leaf infection between *AvrLm1* and *AvrLm4* isolates, with the optimal temperature range for leaf infection being 15–25°C for *AvrLm4* isolates and 10–20°C for *AvrLm1* isolates. These results are supported by a field experiment. The increase of frequency of *AvrLm4* isolates between the leaf infection stage in autumn and the stem canker stage before harvest was greater in a hotter growing season (2002/03) than in a cooler one (2003/04), suggesting that *AvrLm4* isolates may be more fit than *avrLm4* isolates at higher temperatures. Hence, global warming may impact on disease epidemiology and evolution indirectly by changing the shape of pathogen life-history correlations (Evans *et al.*, 2008).

Pathogen local adaptation and host specialization

Adaptation to host genotypes

No parasite exploits all potential host species. Many, if not most, parasites are further restricted in their host range to particular host populations, and even individual host genotypes. Two different levels of host range limitations by parasites have received much attention: specialization on particular species (Futuyma & Moreno, 1988; Joshi & Thompson, 1995) and local adaptation on particular populations (Hoeksema & Forde, 2008; Tack *et al.*, 2012). Both patterns may be the consequence of adaptation to particular host genotypes, and they may arise if there are trade-offs in performance on different host species or populations (Rausher, 1984).

Adaptation to specific host genotypes is expected to arise via a co-evolutionary arms race of host defence and parasite counterdefence. Parasites are expected to have the upper hand because of their larger population sizes, shorter generation times and higher mutation and migration rates compared to their hosts. Hence, parasites are usually expected to be locally adapted to sympatric hosts (Dybdahl & Storfer, 2003; Kawecki & Ebert, 2004). There is considerable support for parasite local adaptation (for reviews, see Hoeksema & Forde, 2008; Tack *et al.*, 2012). Whilst local adaptation via major gene interactions has received considerable attention, far less is known about the ability of pathogens to adapt to quantitative polygenic plant resistances, and the consequences of these potential adaptations on other pathogen life-history traits. Using PVY and two pepper genotypes (one susceptible and one with quantitative resistance), an experimental evolution study showed that adaptation to quantitative resistance was possible and resulted in resistance breakdown. This adaptation was associated with a fitness cost on the susceptible cultivar (Montarry *et al.*, 2012).

Host range

Adaptation to multiple hosts has important implications both for applied and basic research. In recent years, emerging diseases have represented an important threat to agriculture (Anderson *et al.*, 2004). Host specialization represents the reduction in the number of potential host species on which a parasite can successfully survive and reproduce. It is widely accepted that adaptation to a specific host is often coupled with fitness losses in alternative ones (Fry, 1996), and understanding how pathogen life-history trade-offs constrain pathogen host ranges is critical for understanding conditions that enable host shifts. Results of an experimental evolution study of *Tobacco etch virus* demonstrate how trade-offs constrain adaptation. Lineages evolved in novel hosts experienced substantial increases in virulence and virus accumulation in sympatry, but suffered reduced virulence and virus accumulation in the ancestral host. By contrast, lineages evolved in the ancestral host did not increase virulence or viral load on either host (Agudelo-Romero *et al.*, 2008). *Colletotrichum lindemuthianum* is a fungal pathogen of two bean species, *Phaseolus vulgaris* and *Phaseolus coccineus*. An inoculation study comparing infectivity and aggressiveness on local versus allopatric plant–fungus combinations revealed that, for the two fitness traits, a positive correlation between the degree of specialization and the degree of local adaptation was found,

suggesting that host specialization can be reinforced by local adaptation (Sicard *et al.*, 2007).

How costs impact on epidemiological dynamics

Given the penalties of virulence on other life-history traits affecting disease transmission, selection should be expected to eliminate unnecessary virulence from pathogen populations and favour strains with *avr* genes that match the resistance structure of their host population (Vanderplank, 1968). Several studies of agricultural pathosystems support this hypothesis. In tobamovirus populations, virulence-associated costs were supported by field data of pathotype frequencies, with the frequency of virulent types decreasing when the specific pathogenicity was unnecessary (Fraile *et al.*, 2011). In line with predictions of trade-offs maintaining diversity in the presence of resistance (Vanderplank, 1968), higher genetic diversity of the more pathogenic pathotypes was favoured in the presence of resistance alleles but not when most of the host population was susceptible in the field populations (Fraile *et al.*, 2011). When the relative fitness of the *Turnip mosaic virus* (TuMV) isolate UK 1 was compared with more virulent wildtype isolates CZE 1 and CDN 1, the UK 1 outcompeted the virulent isolates in a mixture of susceptible hosts. The observed greater fitness of UK 1 suggests that there may be a fitness cost to TuMV overcoming resistance genes of brassica crops. This may explain the frequency of naturally occurring isolates, in that pathotype 1 isolates are found much more frequently than isolates of other pathotypes (Jenner *et al.*, 2002b). Potentially strong selections against unnecessary virulence, as evidenced by decreased frequencies under field trials, have also been reported for other pathosystems (Leach *et al.*, 2001; Sacristán & García-Arenal, 2008; Bahri *et al.*, 2009).

Far less is known about how trade-offs may impact on disease dynamics in natural populations. The trade-off between virulence and spore production in *M. lini* (Thrall & Burdon, 2003) may explain why populations dominated by particularly infectious strains had lower disease prevalence than populations dominated by avirulent strains (Thrall *et al.*, 2012). Powdery mildew *P. plantaginis* persists as a highly dynamic metapopulation in a large network of host populations of *P. lanceolata* (Laine & Hanski, 2006; Soubeyrand *et al.*, 2009). Susi & Laine (2013) found that positive correlations between virulence and subsequent life-history traits measured on sympatric host plants became negative on allopatric hosts. The epidemiological prediction of this change in life-history relationships in allopatry is lower disease prevalence in newly established pathogen populations. This was confirmed by an analysis of the natural pathogen metapopulation: disease prevalence was lower in newly established pathogen populations and they were more prone to go extinct during winter than older pathogen populations. Hence, life-history trade-offs mediated by pathogen local adaptation may influence epidemiological dynamics at both population and metapopulation levels.

No fitness costs detected – why?

While numerous examples of fitness costs to virulence and other life-history traits have been described in this review, in many other cases the detection of measurable fitness costs has failed. The fitness of the most virulent *Plasmopara viticola* strain was not reduced even on the most susceptible host, suggesting that no costs are associated with virulence (Toffolatti *et al.*, 2012). In the fungal pathogen, *Mycosphaerella graminicola*, experiments demonstrated that the reproductive fitness and virulence of strains were not correlated (Zhan *et al.*, 2002). Unnecessary virulence alleles did not affect fitness of *Blumeria graminis* f. sp. *tritici* (Bronson & Ellingboe, 1986). In addition to not finding correlations, some studies have even detected positive relationships between pathogen virulence and subsequent life-history traits. Montarry *et al.* (2010) found that the latent period was shorter in virulent isolates of *P. infestans*. Similar trends, although not statistically significant, were observed for the other genes tested (Montarry *et al.*, 2010). In four out of five *C. lindemuthianum* populations studied, positive values of local adaptation for both infectivity and aggressiveness were observed, although these correlations were not significant (Sicard *et al.*, 2007). In *P. plantaginis*, life-history traits were positively correlated on sympatric host genotypes, while on allopatric hosts trade-offs appeared.

These findings either suggest that such costs can be low in some pathogens, or that these pathogens evolved compensatory mechanisms to restore the fitness of virulent genotypes. Such compensatory mechanisms have been proposed for *P. infestans* populations collected in French potato production areas where, despite the absence of local selection by the corresponding *R* genes, the same complex virulence phenotypes dominate (Montarry *et al.*, 2010). Bahri *et al.* (2009) also propose that virulence alleles are not selected against because costs are compensated for in the yellow rust pathogen *P. striiformis*. Alternatively, given how condition-dependent trade-offs are (see previously), it is possible that trade-offs may be at play during field epidemics, but the range of abiotic/biotic variation that may impact on their expression is absent from the experimental design. One important biotic component that may strongly impact on disease development, and hence expression of costs, is co-infection. It is becoming increasingly clear that many diseases occur frequently as co-infections (López-Villavicencio *et al.*, 2007; Tollenaere *et al.*, 2012), and hence studying individual strains may fail to capture how disease progresses under field conditions (cf. Zhan *et al.*, 2002). Competition experiments employed by some of the studies reviewed here (Jenner *et al.*, 2002a; Desbiez *et al.*, 2003; Bahri *et al.*, 2007; Janzac *et al.*, 2010; Fraile *et al.*, 2011) allow the disentanglement of how co-infection may impact on trade-offs in pathogens.

Finally, while this review has not tested for publication bias, it is possible that studies that do not find evidence of virulence costs are less likely to have been

published than studies that support the trade-off hypothesis.

Conclusions

Virulence costs are considered major ingredients of the co-evolutionary process because they can prevent all-virulent pathogen genotypes from going to fixation, and thereby preserve genetic diversity in pathogen populations. Moreover, as demonstrated here, pathogen life-history trade-offs play a major role in determining the evolutionary trajectories of pathogens, as they constrain the range of host genotypes and host species which pathogens may adapt to. Costs of virulence are also revealed during the spread of epidemics, as unnecessary *avr* genes impact on disease dynamics at both within-population as well as metapopulation levels.

The problem of *R* gene breakdown following pathogen adaptation, and the increasing threats imposed by emerging and re-emerging diseases, place the study of virulence costs at the heart of both basic evolutionary biology and its applications. A mechanistic understanding of these costs is required for the development of predictive models and the design of prevention strategies to control emerging disease outbreaks. The discovery that temperature may impact on the expression of trade-offs in pathogens suggests that climate change may impact on disease threats in ways that are more complex than what current models predict (Caubel *et al.*, 2012). To date, the results of life-history costs in pathogens are highly variable, and hence, establishing direct links between the fundamental axes of life-history variation, their expression under variable conditions and documenting realized epidemiological dynamics offers an exciting future avenue of research, and is needed to truly validate the relevance of the trade-off theory for pathogens.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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