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*Proc. R. Soc. B* published online 2 May 2012  
doi: 10.1098/rspb.2012.0647

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# The implications of immunopathology for parasite evolution

Alex Best<sup>1,2,\*</sup>, Gráinne Long<sup>3</sup>, Andy White<sup>4</sup> and Mike Boots<sup>2</sup>

<sup>1</sup>*School of Mathematics and Statistics, University of Sheffield, Sheffield S3 7RH, UK*

<sup>2</sup>*Biosciences, College of Life and Environmental Sciences, University of Exeter Cornwall Campus, Penryn TR10 9EZ, UK*

<sup>3</sup>*MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK*

<sup>4</sup>*Department of Mathematics and the Maxwell Institute for Mathematical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, UK*

By definition, parasites harm their hosts, but in many infections much of the pathology is driven by the host immune response rather than through direct damage inflicted by parasites. While these immunopathological effects are often well studied and understood mechanistically in individual disease interactions, there remains relatively little understanding of their broader impact on the evolution of parasites and their hosts. Here, we theoretically investigate the implications of immunopathology, broadly defined as additional mortality associated with the host's immune response, on parasite evolution. In particular, we examine how immunopathology acting on different epidemiological traits (namely transmission, virulence and recovery) affects the evolution of disease severity. When immunopathology is costly to parasites, such that it reduces their fitness, for example by decreasing transmission, there is always selection for increased disease severity. However, we highlight a number of host–parasite interactions where the parasite may benefit from immunopathology, and highlight scenarios that may lead to the evolution of slower growing parasites and potentially reduced disease severity. Importantly, we find that conclusions on disease severity are highly dependent on how severity is measured. Finally, we discuss the effect of treatments used to combat disease symptoms caused by immunopathology.

**Keywords:** immunopathology; parasite evolution; adaptive dynamics

## 1. INTRODUCTION

The damage experienced by hosts when infected with parasites may not only result from the direct effects of parasite growth, but also as a consequence of immune responses in the host. Such immunopathology caused by ‘inappropriate’ host immune responses [1–4] may occur whenever an immune response of the wrong ‘type’ (e.g. for the wrong parasite-killing mechanism) or ‘magnitude’ (e.g. if immune responses are overzealous) is mounted in response to an infection. Some degree of immunopathology may be ubiquitous in parasitic infections [2] resulting from a diverse range of mechanisms, including superantigen expression [5,6], major antigens [7–9] or apoptosis of immune cells [10–12]. Specifically, immunostimulatory superantigens can induce overwhelming cytokine responses that can result in host death via systemic shock [6]; major antigens can induce chronic inflammation, disease and, in some cases, host death [7] and finally, massive apoptosis of immune cells required for pathogen clearance can result in fatal septic shock [12]. Given this ubiquity and the diversity of the underlying mechanisms, it is important to understand the evolutionary implications of immunopathology for infectious disease [4].

Most importantly from an evolutionary perspective, immunopathology may represent an extra source of

mortality to infected hosts, in addition to the background death rate of all hosts and direct parasite-induced mortality/virulence [13]. Acting alone, the mortality owing to the host's immune response would be costly to the parasite, as it further reduces the infectious period, reducing the opportunity for transmission. However, in a recent review [4], a range of systems were identified where host immunopathology has further beneficial effects on parasite fitness. For example, parasites may benefit when immunopathology damages immune cells, preventing clearance of the disease [10,11], or where inflammatory responses boost disease transmission by allowing pathogen persistence in immune-damaged tissue [8,9] or by delaying clearance through immunosuppression [5]. However, as well as mortality due to inappropriate responses, infected hosts may also suffer increased mortality as a cost to mounting what is largely an ‘appropriate’ induced defence [14,15]. In this case, the overall immune response reduces parasite fitness both through direct effects and causing infected host mortality. Given this range of effects on parasite fitness, it is important to examine theoretically the implications of immunopathology for parasite evolution.

The trade-off theory of the evolution of parasites assumes that parasite-induced mortality (virulence) arises as an unavoidable consequence of increased transmission. While this hypothesis has been challenged, it has increasing empirical support and remains the dominant assumption in the evolutionary theory of parasites (see Alizon *et al.* [16] for a recent review of the debate). It is important

\* Author for correspondence ([a.best@shef.ac.uk](mailto:a.best@shef.ac.uk)).

Electronic supplementary material is available at <http://dx.doi.org/10.1098/rspb.2012.0647> or via <http://rspb.royalsocietypublishing.org>.

to note that only a saturating relationship such that transmission becomes increasingly costly in terms of virulence leads to an intermediate optimal transmission and virulence (linear and decelerating trade-offs predict maximization). Under this framework, parasite virulence is expected to increase until such a point that any benefit from increased transmission is outweighed by the cost of a reduced infectious period [17–20]. Day *et al.* [13] showed theoretically that if immunopathology is independent of, or decreases with, exploitation, the parasite will increase its investment in exploitation, while if immunopathology increases with parasite exploitation, then the parasite will decrease its investment. Gilchrist & Sasaki [15] developed a general host–parasite model where they assumed a mortality cost to the host of mounting an immune response. They found that more costly immune responses tended to favour lower parasite growth rates, as increasing replication rates triggered much greater immune responses in the host and therefore much greater mortality. Here, we build on this theoretical work by linking the level of immunopathology, defined as mortality induced by the host’s immune response, to the epidemiological traits of transmission, virulence and recovery. In this way, we can model a wide range of realistic relationships between parasite fitness and immunopathology. Making the standard assumption of trade-offs in the parasite, we investigate how selection on parasite growth is affected as the level of immunopathology varies. Furthermore, we consider the effects of both the immunopathology and the evolutionary optimal level of parasite growth on measures of disease severity.

## 2. METHODS

We investigate the effects of mortality due to the host’s immune response on a classic susceptible–infected–susceptible model [21], where the dynamics of susceptible and infected hosts are described by the equations

$$\left. \begin{aligned} \frac{dX}{dt} &= aX - qX(X + Y) - bX - \beta XY + \gamma Y \\ \frac{dY}{dt} &= \beta XY - (\alpha + b + \gamma)Y - pY. \end{aligned} \right\} \quad (2.1)$$

Hosts are born susceptible at birth rate  $a$ , which is reduced owing to crowding by  $q$ , and die at natural death rate  $b$ . Transmission is a mass action term occurring at rate  $\beta$ . Once infected, hosts may die naturally or through disease-induced virulence,  $\alpha$ , or they may recover back to susceptibility at rate  $\gamma$ . The key component of our model is that we add an additional death term associated with the host’s immune response, which we define as immunopathology,  $p$ .

Following classic models of parasite evolution, we assume that transmission and virulence are fundamentally linked to the parasite’s exploitation rate,  $\varepsilon$  (figure 1). In particular, we assume that virulence increases linearly with exploitation, while transmission is an increasing but saturating function. This yields the classic saturating trade-off between transmission and virulence required for an intermediate evolutionary optimum. As well as being more infective and more damaging, high parasite growth rates may also make infections harder to clear. If this occurs, there is an additional potentially important trade-off for the parasite between virulence and recovery rate [17,19,22]. Although the transmission–virulence trade-off

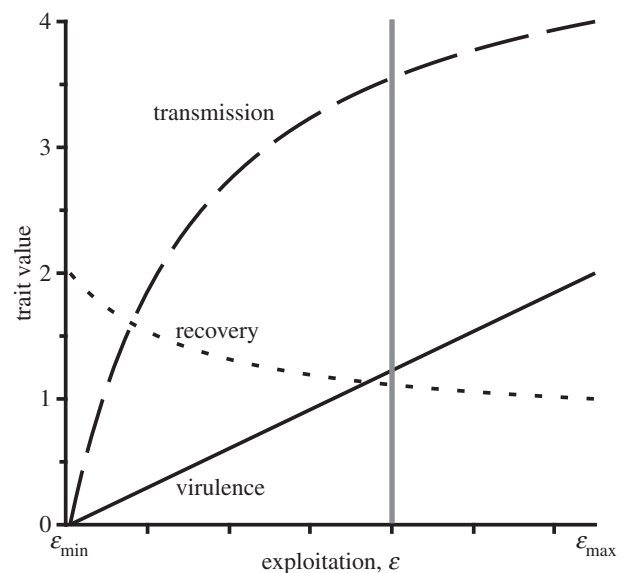


Figure 1. Trade-offs of virulence (solid line), transmission (dashed line) and recovery (dotted line) with exploitation rate. The trade-offs are of the form,  $\tau = \tau_{\max} - (\tau_{\max} - \tau_{\min})(1 - (\varepsilon - \varepsilon_{\min})/(\varepsilon_{\max} - \varepsilon_{\min})) / (1 + m(\varepsilon - \varepsilon_{\min})/(\varepsilon_{\max} - \varepsilon_{\min}))$ , linking the maximum and minimum trait values, with the shapes governed by the parameter  $m$ . The extremes of  $\varepsilon$  are chosen such that in all the models the continuously stable strategy investment at  $p = 0$  is  $\varepsilon = 1$ , at the point marked by the grey line. The values used are  $(\varepsilon_{\max}, \varepsilon_{\min}) = (1.5, 0.21)$ ,  $(\beta_{\max}, \beta_{\min}) = (4, 0)$ ,  $m_{\beta} = 4$ ,  $(\alpha_{\max}, \alpha_{\min}) = (2, 0)$ ,  $m_{\alpha} = 0$ ,  $(\gamma_{\max}, \gamma_{\min}) = (1, 2)$ ,  $m_{\gamma} = 4$ . Note: maximum and minimum values of recovery are reversed to produce a decreasing function.

has received considerably more attention, this recovery–virulence trade-off does have empirical support, particularly from the classic myxomatosis studies of Fenner & Ratcliffe [23], and is the focus of the classic theoretical study on the coevolution of parasites by Anderson & May [17]. We therefore also assume that the recovery rate decreases with increasing exploitation as a saturating function (figure 1). It is also conceivable in some circumstances that higher parasite growth rates lead to a stronger immune response in the host and therefore faster clearance of the parasite. However, this would not be a recovery–virulence trade-off from the point of view of the parasite but a more general transmission–infectious period trade-off. In this case, parasites would be selected to decrease their growth rate in order to lengthen the infectious period by both reducing virulence and recovery rate. (We note here that as long as the general saturating shapes of the transmission and recovery trade-offs are retained, our results are qualitatively robust to changes to their exact shapes in figure 1.)

In addition to these parasite trade-offs, we also assume that the epidemiological traits of virulence, transmission and recovery ( $\alpha, \beta, \gamma$ ) may be linked to the level of immune-induced mortality. As such, these terms are expressed as  $\beta(\varepsilon, p)$ ,  $\alpha(\varepsilon, p)$  and  $\gamma(\varepsilon, p)$ . (We do not explicitly consider here cases where virulence is linked to immunopathology, thus  $\alpha(\varepsilon, p) = \alpha(\varepsilon)$ .)

In our evolutionary analysis, we take an adaptive dynamics approach [24], assuming that a rare mutant parasite strain with exploitation rate  $\varepsilon_m$  attempts to invade a resident strain (with exploitation rate  $\varepsilon$ ) at equilibrium.

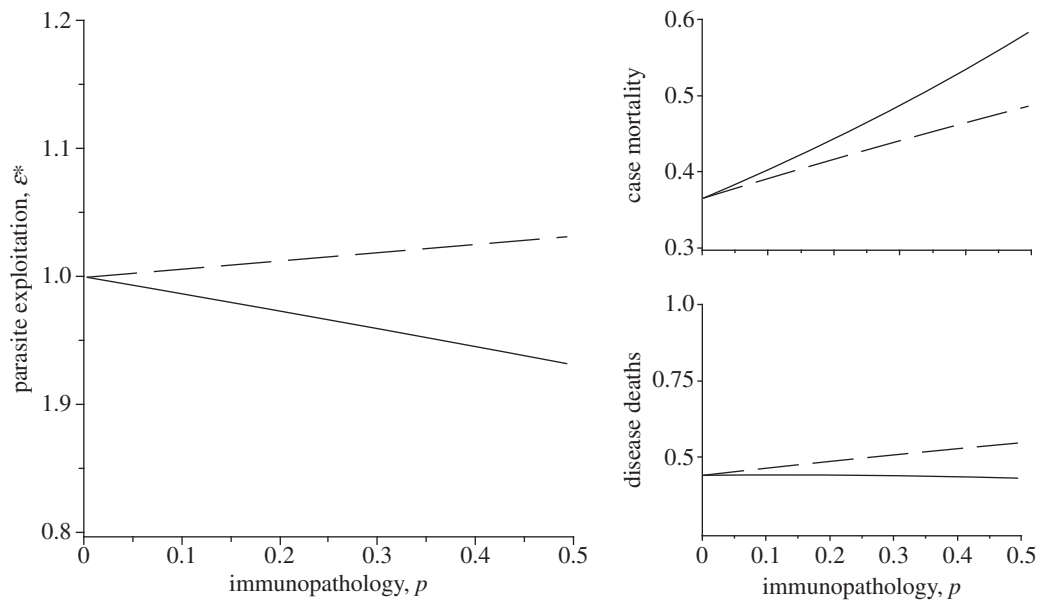


Figure 2. The effect on parasite exploitation when increased immunopathology (IP) leads to reduced recovery. The parasite invests in slightly lower exploitation as IP increases. This leads to much greater case mortality and slightly reduced disease-induced deaths. Parameter values are as of figure 1, and:  $a = 2$ ,  $q = 0.1$ ,  $b = 1$ .

The mutant parasite's success depends on its invasion fitness, defined as its initial growth rate, given by

$$r = \beta(\varepsilon_m, p)X^* - (\alpha(\varepsilon_m, p) + b + \gamma(\varepsilon_m, p) + p), \quad (2.2)$$

where  $X^* = (\alpha(\varepsilon, p) + b + \gamma(\varepsilon, p) + p)/\beta(\varepsilon, p)$  is the equilibrium host density for the resident parasite strain. If  $r > 0$ , then the mutant will invade to coexist with or replace the resident strain. If  $r < 0$ , then the mutant strain cannot invade and will die out. Through a series of mutations and substitutions, the parasite will evolve its exploitation rate until it reaches an 'evolutionarily singular point', a (potentially temporary) 'stopping point' of evolution. Provided this point is both evolutionarily stable (locally uninvadible) and convergence-stable (locally attracting), this will be a long-term attractor of evolution, often called a continuously stable strategy (CSS; [25,26]—see electronic supplementary material). We can then investigate how the CSS level of parasite exploitation changes as the rate of immunopathology in infected hosts is varied when it is linked to different epidemiological traits, both with negative and positive effects on the parasite. Owing to the complexity of including three trade-offs, we conduct our analysis numerically (that is, we choose values for all parameters except the evolving traits and fix the trade-offs as described in figure 1, then locate the singular points as normal).

We first examine cases where host immunopathology benefits the parasite (through reduced recovery and increased transmission). We then move on to consider cases where the induced immune defences damage the parasite further to the mortality cost (through increased recovery). We have defined immunopathology to be the increased mortality rate induced by the host's immune response, whether that response benefits or damages the parasite. It may, of course, be questioned whether 'immunopathology' is suitable nomenclature for an immune response that appropriately damages parasite fitness, but for clarity, we take this simple definition throughout this paper. For simplicity, we shall assume simple linear relationships, e.g.  $\beta(\varepsilon, p) = \beta(\varepsilon) + cp$ , where  $c$  controls the strength of the effect of immunopathology (nonlinear

relationships produce qualitatively similar results—see electronic supplementary material). We shall consider cases where the strength of the relationship is weak ( $c = 0.5$ ) and strong ( $c = 2$ ). For clarity, we choose parameters such that when there is no immunopathology ( $p = 0$ ), the parasite will exploit at exploitation rate  $\varepsilon = 1$ , meaning we can simply consider the relative increase or decrease in exploitation as immunopathology increases. In each case, we find the CSS level of exploitation for the parasite for varying levels of host immunopathology. While evolutionary models tend to focus on the level of parasite virulence, a range of measures may be used to consider disease severity in natural and experimental host–parasite interactions. Here, we consider the combined effect of both the mortality itself and the CSS exploitation on two realistic measures of disease severity:

- case mortality (the proportion of infections resulting in death due to disease;  $(\alpha + p)/(\alpha + b + \gamma + p)$ ).
- disease-induced deaths (the number of deaths due to disease over some time period);  $(\alpha + p)Y$ , where  $Y$  is the equilibrium density of infected hosts).

Both of these measures may be relatively easily calculated from data on host–parasite systems, and will allow us to understand how the combination of immunopathology and the evolved parasite exploitation will affect the population-level severity of disease.

### 3. RESULTS

#### (a) Immunopathology increases parasite fitness

We first assume that immunopathology benefits the parasite, and in particular that increased immunopathology leads to a reduction in clearance (which lengthens the infectious period). In figure 2, we show how increasing  $p$  then affects the parasite exploitation rate, and the consequent effect on the two measures of disease severity (case mortality and disease deaths), where dashed lines assume a weak effect of immunopathology on recovery ( $c = 0.5$ ) and solid lines a strong effect ( $c = 2$ ). The effect of increased  $p$  on parasite exploitation depends on

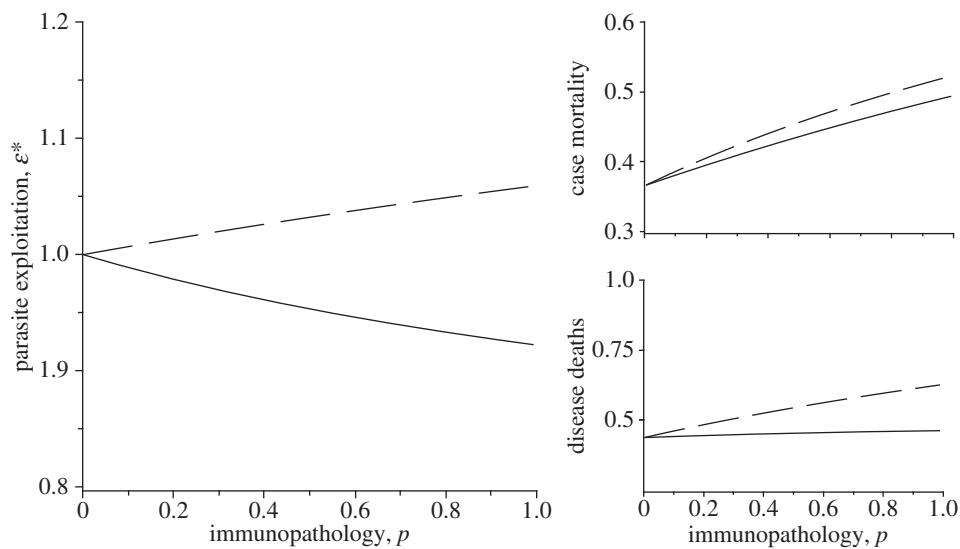


Figure 3. The effect on parasite exploitation when increased IP leads to increased transmission. Effects where there is a strong (solid line) or weak (dashed line) linear relationship. The parasite invests in much less exploitation as IP increases when the effect is strong, but is more when the effect is weak. This leads to greater case mortality in both cases, but disease-induced deaths decrease when the effect is strong and increase when the effect is weak. Parameter values are as of figures 1 and 2.

the strength of the effect. If the effect is weak, there is a small rise in exploitation rate, but once the effect becomes reasonably strong the parasite is selected to reduce its exploitation (note, higher values of  $p$  cannot be reached as the recovery rate would become negative for  $c = 2$ ). The increase in immunopathology, combined with the parasite's lowered exploitation strategy, leads to only small changes in the number of disease deaths as the two effects roughly balance. However, there are relatively large increases in the case mortality as the recovery rate decreases more quickly than immunopathology, and this effect becomes more pronounced the stronger the effect of immunopathology.

We also investigate the effect of immunopathology when it leads to increased transmission. Here, we again assume a linear effect of immunopathology, with either a strong effect of immunopathology on transmission (figure 3, solid line) or a weak effect (figure 3, dashed line). When this effect is strong (solid line), the benefit of increased transmission outweighs the damage of immunopathology, resulting in a net increase in parasite fitness. The parasite therefore decreases its exploitation rate, with an increasingly steep drop, the greater the strength of immunopathology (not shown). This again leads to a relatively large increase in case mortality but little change in the number of disease deaths (stronger effects will lead to a decrease in disease deaths—not shown). A weaker link to immunopathology leads to a shallower effect, with exploitation in fact increasing if the effect is too weak (dashed line). This leads to an even greater rise in case mortality, as the recovery rate does not reduce as significantly with the lessened change in exploitation, and also means the number of disease deaths increases.

#### (b) Immunopathology reduces parasite fitness

We finally assume that increased induced defences in the host, which are damaging to the parasite, also induces increased immunopathology in the infected individuals as a cost of mounting the immune response. We focus on the case where immunopathology is correlated with

increased recovery from infection (figure 4). Increased immunopathology selects for significantly increased parasite exploitation, with a considerable increase in investment when the effect of immunopathology is strong. As immunopathology increases, there is a small rise in the case mortality as the ratio of recovery to immunopathology stays roughly similar, but a significant increase in disease deaths due to the additional virulence caused by increased exploitation.

## 4. DISCUSSION

By reducing the infectious period through increased host death rate, immune-induced mortality causes a direct fitness cost to parasites. Where immunopathology has beneficial effects on parasite fitness, for example by increasing the infectious period through reduced recovery rates, or increasing transmission, then the evolutionary response of the parasite depends on the strength of these benefits relative to the increased host mortality of the immunopathology itself. In particular, if the beneficial effects on parasite fitness are high relative to any increased mortality, then the evolution of decreased parasite exploitation rate is expected. This may result in the evolution of decreased disease severity when measured as disease-induced deaths, but increased severity in terms of case mortality. It should be noted that when immunopathology positively affects parasite fitness with negligible effects on host mortality, there will be selection for milder disease. In contrast, where immunopathology only reduces parasite fitness, for example by reducing the infectious period or the growth rate of the parasite, our models show that there is always strong selection for the parasite to increase exploitation. This increase in exploitation counters the loss in parasite fitness caused through mortality by increasing transmission and/or reducing recovery. The relative effects of immunopathology on epidemiological traits are therefore critical in determining the evolution of severity of infectious disease.

Immunopathology has been found to have a profound effect on parasite fitness in a range of host–parasite

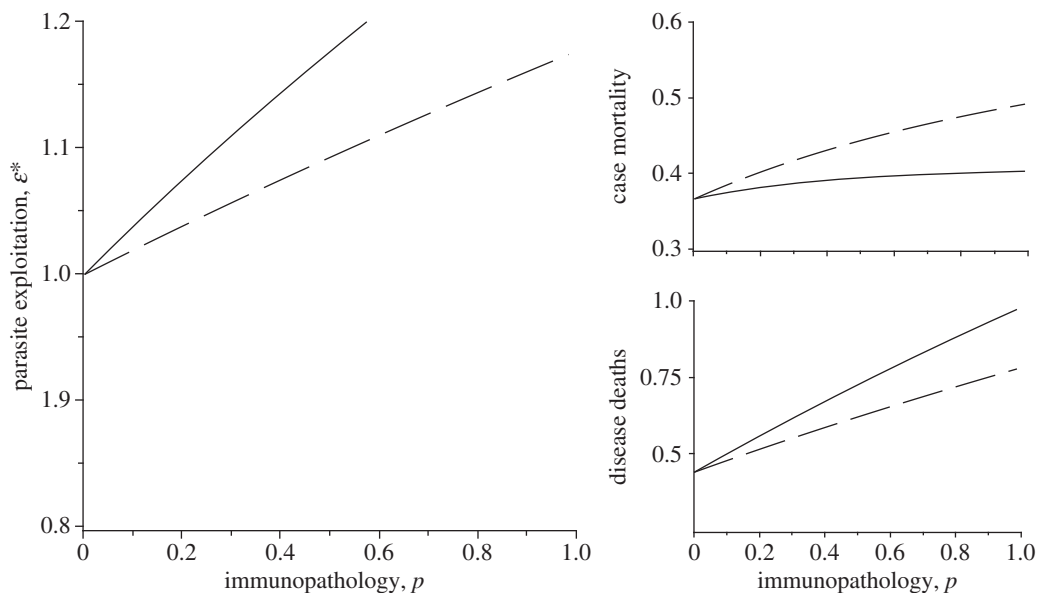


Figure 4. The effect on parasite exploitation when increased IP leads to increased recovery. The parasite invests in much greater exploitation as IP increases (main plot). This leads to lower disease prevalence, a slightly higher case mortality and greater disease-induced deaths (subplots). Parameter values are as of figures 1 and 2.

systems [4]. Often, immunopathology is costly to parasites due to a reduction in the infectious period through an increase in host death, for example through septic shock [12]. However, there are also a range of effects that are beneficial to the parasite, for example by reducing recovery from disease [10,11] and thus increasing the infectious period, or by increasing transmission [8,9]. Our results suggest that immunopathology is a potentially powerful selective force, which may act to alter parasite exploitation strategies in response to these epidemiological effects. However, the direction of selection may be sensitive to the relative costs and benefits the parasite experiences. Therefore, details of the correlations between immunopathology and general epidemiological traits in particular systems must be taken into account when predicting the evolution of parasites.

Our models give a number of predictions for the role of immunopathology in a number of specific infectious diseases. Where immunopathology is purely correlated negatively with parasite fitness, for example during *Staphylococcus aureus*, *Histoplasma capsulatum* and *Bacillus anthracis* infections [4], we would expect selection for increased levels of exploitation through immunopathology. However, the role of immunopathology in a wide range of diseases, including *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Listeria monocytogenes* and *Toxoplasma gondii*, where there are some positive fitness correlations [4], is dependent on both the strength of these correlations and any costs of immunopathology due to increased host mortality. Understanding the relative fitness costs and benefits of immunopathology in these systems, as well as the evolutionary trade-offs between epidemiological traits, is therefore critical to understanding the role of immunopathology during parasite infection and may vary according to the exact parasite in question.

Immunopathology, as a general immunological term, is understood to simply account for any damage caused to the host through the activation or function of its

immune response. This damage is often measured experimentally in terms of tissue damage, but not explicitly linked to changes in mortality. In our models, we assume that immunopathology causes an increased mortality to infected hosts, resulting in a reduced infectious period. It is therefore important to understand how these measures of damage recorded in experiments may translate to ecological traits such as mortality and fecundity if we are to fully understand the effects that immunopathology will have on parasite evolution. Laboratory models of diseases such as *S. pyogenes*, *S. pneumoniae*, *M. tuberculosis*, *L. monocytogenes* and *T. gondii*, where the immunopathology has beneficial effects on parasite fitness may not record (or allow) host mortality. If there is no or negligible mortality due to the specific immunopathological effects in these system, there will always be selection for less disease severity.

For the management of infectious disease, it is important to understand the effect that immunopathology and the resultant change in parasite exploitation will have on the population-wide severity of the disease. While theoretical models often focus on virulence, the rate of pathogen-induced death, in many cases alternative measures of disease severity such as case mortality and the number of deaths due to disease may be more appropriate [27]. We have examined how these measures of disease burden are affected by immunopathology directly and the evolution of the parasite. An intuitive result is that however immunopathology affects the epidemiology of the host–parasite interaction, if it causes increased mortality, it always leads to an increase in case mortality. However, the strength of the increase in case mortality will vary depending on whether virulence due to parasite growth is correlated with immunopathology. In most cases, mortality due to the immune response also causes an increase in disease-induced deaths, but when there are significant benefits to the parasite from immunopathology, then the overall number of deaths may decrease. Therefore, interventions that reduce

immunopathology may successfully reduce the case mortality of a disease, but may, as a consequence, increase the number of deaths. Our interpretation of the effectiveness of any treatments may therefore be extremely sensitive to the measure of severity that is used. Empirical and experimental studies of host–parasite interactions must therefore be clear on how disease severity is measured in their system and on how this may be related to the underlying selection on the parasite. Clearly, it is crucial for the development of informed management strategies that the relative costs and benefits associated with immunopathology are well understood in important disease interactions.

The implications of immunopathology for parasite evolution have received very little attention in the theoretical literature, with a key exception being the study of Day *et al.* [13]. They too investigated how immunopathology, defined as an increased mortality rate, affected selection on the parasite under a transmission–virulence trade-off. In particular, they assumed that immunopathology may be directly linked to parasite exploitation, with more exploitative parasites inducing higher, lower or equal levels of immunopathology in the host. In contrast, we have assumed that immunopathology, while infection-induced, is a standard host response to being infected. We have then assumed that this immunopathology may affect selection on the parasite by altering various epidemiological traits, but not being directly linked to parasite exploitation. An important extension to this work would be to consider the more complex scenario where there is both a direct correlation between parasite exploitation and immunopathology, as well as the links between immunopathology and epidemiological traits.

While we have focused here on the effects that immune-induced mortality may have on the parasite, there are also likely to be strong selective pressures on the host [2]. We have implicitly assumed here that a more robust immune response in the host incurs a cost of increased mortality in infected hosts, and is therefore linked to resistance or tolerance mechanisms to parasitism. However, we have not considered the evolutionary dynamics of this relationship explicitly, and therefore we do not know under what circumstances immunopathology is likely to evolve as a host strategy in the first place. Gilchrist & Sasaki [15] found that when host immune response (leading to faster clearance of the parasite) induces a mortality cost, host investment increased slower than linearly with parasite replication rate, suggesting that immune-induced mortality will be higher against more exploitative parasites. More generally, there is a considerable body of theory on the evolutionary dynamics of host defence in response to parasitism [20,28–30] highlighting the dependence of host defence on both epidemiological and general life-history traits, as well as on the nature of the costs to defence. Given our results, it is important to understand under what circumstances hosts are selected to exhibit immune-induced mortality and, indeed, to investigate coevolutionary outcomes.

While immunopathology is well understood as an important component in the management of infectious diseases in the biomedical literature, there remains little understanding of its characteristics in an epidemiological and evolutionary framework. Our work builds on previous theoretical work [13,15] to show how immunopathology may have a profound effect on the evolutionary dynamics

of a parasite. Further theoretical and in particular empirical work is needed to gain a more detailed understanding of the evolutionary effects of immunopathology on both parasites and their hosts.

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