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# Parasite evolution in response to sex-based host heterogeneity in resistance and tolerance

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dimorphism;  
epidemiology;  
resistance;  
tolerance;  
transmission;  
virulence.

## Abstract

Heterogeneity between sexes in terms of both the level and the type of immune response to infection is documented in many species, but its role on parasite evolution is only beginning to be explored. We adopt an evolutionary epidemiology approach to study how the ability of a host to respond to infection through active immunity (resistance) or through minimizing deleterious effects of a given parasite load (tolerance) affects the evolution of parasite virulence. Consistently with earlier models, we find that increases in host resistance and tolerance both favour more virulent parasite strains. However, we show that qualitatively different results can be obtained if dimorphism between the sexes occurs through resistance or through tolerance depending on the contact pattern between the sexes. Finally, we find that variations in host sex ratio can amplify the consequences of heterogeneity for parasite evolution. These results are analysed in the light of several examples from the literature to illustrate the prevalence of sexually dimorphic immune responses and the potential for further study of the role of sexual dimorphism on parasite evolution. Such studies are likely to be highly relevant for improving treatment of chronic infections and control of infectious diseases, and understanding the role of sex in immune function.

## Introduction

Many parasites are public health or agronomical threats because they evolve rapidly. Understanding how heterogeneity among the hosts they can infect affects this evolution is an actively growing area of research (e.g. Regoes *et al.*, 2000; Gandon, 2004; Osnas & Dobson, 2011; Williams, 2012). Heterogeneity in host immunity may be reflected in various aspects of infection, including frequency, duration, parasite load and observed levels of immune response (Zuk & McKean, 1996; Rolff, 2002; Nunn *et al.*, 2009; McClelland & Smith, 2011).

One type of heterogeneity that seems to have been largely overlooked by evolutionary parasitologists is sexual dimorphism. Males and females of many organisms are generally susceptible to infection by the same

parasites, yet often show clear differences in either the strength or the type of immune response or both (see e.g. Klein, 2004). This distinction between types of immune response is apparent if one considers the virulence of an infection, that is the decrease in host fitness due to the infection (Read, 1994). When confronted with a parasite, the immune response of the host can be quantified in terms of its ability to mitigate virulence either by avoiding infection or directly reducing parasite growth (resistance) and by its ability to limit damage caused by a given parasite load (tolerance) (Boots *et al.*, 2009; Råberg *et al.*, 2009; Little *et al.*, 2010; Ayres & Schneider, 2012). Both resistance and tolerance can occur through a variety of mechanisms and are predicted to affect parasite evolution in different ways: in general, resistance and tolerance are both expected to select for more virulent parasites (Boots *et al.*, 2009; Little *et al.*, 2010), but details can affect this outcome (Gandon & Michalakis, 2000; Miller *et al.*, 2006).

Despite numerous empirical examples, the role that sex-based immune heterogeneity plays in parasite

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**Table 1.** Empirical support for sexual dimorphism in resistance and tolerance. M<sup>g</sup> refers to males that have been surgically castrated (gonadectomized). M<sup>s</sup> refers to strain-specific immune responses (in males). Tolerance is broadly identified by an anti-inflammatory (IL-4, 5, 10) T<sub>H</sub>2-type response, and/or higher parasite loads *without* a marked increase in mortality. Resistance is marked by a strong pro-inflammatory (IF- $\gamma$ , T<sub>H</sub>1-type response), with lower mortality and/or severity of disease.

| Parasite   | Host  | Dimorphism   | Tolerate | Resist         | References   |
|--|---|--|----------|----------------|--|
| <b>Bacteria</b>  |   |  |          |                |  |
| <i>Borrelia burgdorferi</i> (Lyme disease)                 | Humans                                      | F: higher susceptibility to reinfection and anti-inflammatory response*<br>M: clear more effectively   | F        | M              | Jarefors <i>et al.</i> (2006)  |
| <i>Vibrio vulnificus</i> bacterium                         | Rats, humans                                | M: Higher rates of infection and mortality; oestrogen injection mitigates disease severity (rats)  |          | F              | Humans (Kuo Chou <i>et al.</i> , 2010); rats (Merkel <i>et al.</i> , 2001)                           |
| <b>Fungi</b>   |   |  |          |                |  |
| <i>Cryptococcus neoformans</i>                             | Humans                                      | M: more susceptible and carry higher splenic fungal burdens<br>F: higher early cytokine response; no difference between sexes in mortality or acute fungal burden                                      | M        | F              | Bava & Negrone (1992); Lortholary <i>et al.</i> (2002)   |
| <i>Candida albicans</i>                                    | Humans                                      | F: more frequently infected, with higher fungal loads (in HIV <sup>+</sup> patients)   | F        |                | White & Larsen (1997)  |
| <i>Paracoccidioides brasiliensis</i>                       | Humans, <i>Mus musculus</i>                 | M: higher fungal load; infected 10–13 $\times$ more frequently despite equivalent exposure rates<br>F: launch more effective antifungal response and higher nitric acid                                | M        | F              | Restrepo <i>et al.</i> (2008); Pinzan <i>et al.</i> (2010)   |
| <i>Mycobacterium marinum</i>                               | <i>Mus musculus</i>                         | M: more susceptible to infection; higher mortality, more lesions, higher parasite loads and decreased antibody production<br>F: clear infection more rapidly and effectively                           |          | F              | Yamamoto <i>et al.</i> (1991)  |
| <b>Macroparasites</b>                                      |   |  |          |                |  |
| <i>Schistosoma mansoni</i> and <i>S. haematobia</i>        | <i>Mus musculus</i> (House mouse)           | F: develop more adult worms, experience higher mortality, infection severity and mortality mediated by testosterone  |          | M              | Eloi-Santos <i>et al.</i> (1992); Nakazawa <i>et al.</i> (1997)                                      |
| <i>Schistosoma mansoni</i>                                 | Humans                                      | M: infected more frequently, greater incidence of more severe hepatic fibrosis; higher IgA levels (chronic infection)  |          | F              | Mohamed-Ali <i>et al.</i> (1999); Degu <i>et al.</i> (2002)  |
| <i>Schistosomiasis haematobia</i> (chronic)                | Humans                                      | F: elevated IL-10 and TGF- $\beta$ profiles (inhibition of T <sub>H</sub> 1-type cytokines TNF- $\alpha$ and IFN- $\gamma$ ); high IgA (chronic infection)   | F        | M              | Remoué <i>et al.</i> (2001)  |
| <i>Toxoplasma gondii</i>                                   | <i>Mus musculus</i>                         | M: Elevated IL-12 and IFN- $\gamma$ production<br>F: mortality higher  |          | M              | Walker <i>et al.</i> (1997)  |
| <i>Babesia microti</i>                                     | <i>Mus musculus</i>                         | M: (certain immunocompromised strains) reduced mortality and parasite loads relative to females  |          | M <sup>s</sup> | Aguilar-Delfin <i>et al.</i> (2001)  |
| New World <i>Leishmania major</i> and <i>L. mexicana</i>   | <i>Mus musculus</i>                         | F: <i>L. major</i> lesions do not heal; resistance (increased IFN- $\gamma$ ) to <i>L. mexicana</i> infection<br>M: highly susceptible (T <sub>H</sub> 2-mediated reaction)                            | M        | F              | Alexander (1988); Travi <i>et al.</i> (2002); Lezama-Davila <i>et al.</i> (2007)                     |
| <i>Plasmodium chabaudi</i> and <i>P. berghei</i> (malaria) | Humans, <i>Mus musculus</i>                 | M: higher parasite loads, severity of infection and (in mice) mortality<br>F: more antibodies and IFN- $\gamma$ ; testosterone decreases antibodies and increases splenic CD8 <sup>+</sup> lymphocytes |          | F              | Wunderlich <i>et al.</i> (1991); Benten <i>et al.</i> (1992, 1993, 1997); Zhang <i>et al.</i> (2000) |
| <i>Hypoderma tarandi</i>                                   | <i>Rangifer t. tarandus</i> (Peary caribou) | F, M <sup>g</sup> : lower fly larvae prevalence than intact males  |          | F              | Folstad <i>et al.</i> (1989)   |

Table 1. (Continued)

| Parasite   | Host   | Dimorphism  | Tolerate | Resist | References  |
|--|--|---|----------|--------|---|
| <i>Taenia crassiceps</i> and <i>T. taeniformis</i> | Humans, <i>Mus musculus</i>                                    | F: greater severity of infection, for example number of cysts, and inflammation surrounding cysts; higher IL-6, IL-5 and IL-10 concentrations; in mice, higher IL-4 and IFN- $\gamma$ ; associated with later immunity; oestradiol increases parasite reproduction; infection-induced male feminization | M        |        | Lin <i>et al.</i> (1990); Larralde <i>et al.</i> (1995); Chavaria <i>et al.</i> (2005); Guzmán <i>et al.</i> (2009); Kelvin <i>et al.</i> (2009)        |
| Viruses  |  |   |          |        |   |
| Cytomegalovirus                                    | Humans   | F: higher prevalence of infection; elevated responses (higher secreted IL-2, and frequency of secreting cells and IL-2 responders)  |          |        | Villacres <i>et al.</i> (2004); Simon <i>et al.</i> (2013)  |
| Influenza A  | Humans (co-infected with CMV)                                  | Similar memory responses to infection<br>M: infected more frequently and severely; significantly higher TNF- $\alpha$   |          | F      | Villacres <i>et al.</i> (2004)  |
| Vesicular stomatitis                               | <i>Mus musculus</i><br>BALB/c and<br>BALB/c-H-2 <sup>dm2</sup> | F: higher IFN- $\gamma$ and IL-2 (elevated $T_H1$ response)<br>F: lower viral titres (up to 2–4 log <sub>10</sub> ); reduced migration between brain regions; elevated immunoreactive nitrous oxide (nNOS) production; greater recovery   |          | F      | Barna <i>et al.</i> (1996)  |
| Human immunodeficiency virus (HIV)                 | Humans   | M: higher viral loads during asymptomatic infection<br>F: duration of asymptomatic infection shorter  | M        | F      | Napravnik <i>et al.</i> (2002); Donnelly <i>et al.</i> (2005); Nicastrì <i>et al.</i> (2005); Prins <i>et al.</i> (2005); Langford <i>et al.</i> (2007) |

\*IL-4:IFN- $\gamma$  and IL-10:TNF- $\alpha$  ratios.

evolution is only beginning to be explored (Duneau & Ebert, 2012), although some studies have sought to address the evolution of sexual dimorphism in immunity in a general sense, and from the perspective of the host (Restif & Amos, 2010; McClelland & Smith, 2011). In Table 1, we highlight some of the existing data showing how sexes can differ both in the intensity of their immune response and also in the type of immune response (tolerance vs. resistance). Sex-specific immune differences are frequently mediated by the sex steroid hormones (i.e. androgens, oestrogens and progesterones, Klein *et al.*, 2000). Widespread patterns are thus observable across infections arising from a wide range of disease agents; in general, females seem to more actively resist infection and launch a stronger antiparasitic immune response once infected, whereas males exhibit a higher susceptibility to initial infection and increased ability to tolerate sustained infection once infected.

Several theoretical studies have considered the effect of host heterogeneity on the evolution of parasite traits, especially virulence. These studies are based on epidemiological models with several host classes (Diekmann & Heesterbeek, 2000). One of the earliest models is that by Regoes *et al.* (2000) for parasites with a free-living stage. By assuming that there exists a negative correlation between virulence in one host type and virulence in the other host type, they find that heterogeneity selects for lower virulence, which can be interpreted as a generalist strategy. Only when they allow for parasite within-host evolution do they find polymorphism in the parasite population. Gandon *et al.* (2002) also model host heterogeneity in the context of a gene-for-gene setting (hosts are either susceptible or resistant to the disease) and show striking co-evolutionary patterns between infectivity (the ability for the parasite to circumvent host resistance) and virulence. Gandon (2004) developed a general framework to study the trait evolution of multihost parasites. This general framework allows for a variable number of hosts and trade-offs between parasite traits expressed in each host type and does not make any *a priori* assumptions concerning trade-offs between traits. The main limitation of this framework is its generality: it is difficult to get an intuition as to how parasite traits should evolve in specific settings. Two recent models involve host heterogeneity. Osnas & Dobson (2011) apply Gandon (2004)'s framework to the case of emerging diseases, with a reservoir host and a new host. They improve the framework by allowing for trait values to vary over the course of an infection (similarly to Day, 2001). They find that, although large mutation steps can allow for dimorphic parasite populations to coexist, there is no evolutionary branching. This contrasts with the result obtained by Gandon (2004), which they attribute to their assumption that transmission is frequency dependent (Gandon assumes density-dependent transmission). Williams (2012) develops a framework that

allows for increasing the number of host types while keeping a simple and intuitive framework. He shows how this allows interpretation of earlier results in a more general setting. Finally, note that the epidemiological Price equation framework can also allow study of short-term parasite evolutionary dynamics in a diverse host population (Gandon & Day, 2009).

We build a mathematical model based on a classical evolutionary epidemiology framework (Gandon, 2004; Osnas & Dobson, 2011) and use it to investigate how host heterogeneity and contact patterns between hosts affect parasite evolution. The originality of our model is that it incorporates the distinction between resistance and tolerance to explore how both the level and the type of heterogeneity make a difference in parasite virulence evolution. We also vary patterns of contact between host types. Our model is generic and may be applied to any type of dimorphism between hosts. However, we analyse it with a sex-specific perspective to illustrate connections with empirical examples that support sexual dimorphism in resistance and tolerance (Table 1). Although heterogeneity may exist on many levels, we focus our investigation on resistance and tolerance because for these aspects of immunity, theory has postulated distinct evolutionary predictions (Gandon & Michalakis, 2000; Miller *et al.*, 2006); they can be described mechanistically and empirically and have not been previously addressed in other models with host heterogeneity (explicitly or implicitly). We show that the distinction between resistance and tolerance is important in determining outcomes of parasite evolution and that both the strength and the type of heterogeneity matter.

## The model

### The epidemiological setting

For simplicity, we adopt the perspective that tolerance and resistance are primary features of the host, and virulence and transmission are features of the parasite. Of course, in reality, all these traits are the result of a  $G \times G \times E$  interaction, that is between host genotype, the parasite genotype and the environment. We start from a basic epidemiological model, which involves tracking changes in densities of susceptible ( $S$ ) and infected ( $I$ ) individuals (Anderson & May, 1991). We therefore focus on persistent infections from which hosts do not recover, for example HIV infections. The epidemiological dynamics of the system are governed by the following set of ordinary differential equations (ODEs):

$$\frac{dS}{dt} = \varphi(S, I) - \beta(\alpha)SI - \mu S \quad (1a)$$

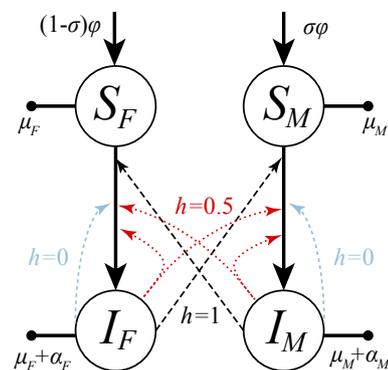
$$\frac{dI}{dt} = \beta(\alpha)SI - (\mu + \alpha)I \quad (1b)$$

where  $\varphi(S, I)$  is the input rate of new susceptible hosts,  $\beta$  is the parasite transmission rate,  $\mu$  is the host base-

line mortality rate and  $\alpha$  is the intrinsic virulence, that is the disease-induced host mortality. To limit potentially confounding feedbacks from host population dynamics on parasite evolution, we assume a constant host population size such that  $\varphi(S, I) = \mu N + \alpha I$ , where  $N$  is the total (constant) host density (i.e.  $N = S + I$ ). The same system has been used as a simple way to capture the epidemiology of HIV as there is no recovery, and transmission can be frequency dependent because the host population size is constant (Anderson & May, 1991).

As in most virulence evolution models, we assume a trade-off relationship between the rate at which a pathogen transmits from a host and the duration of the infection, that is the inverse of virulence (Anderson & May, 1982; Ewald, 1983; Alizon *et al.*, 2009). This trade-off relationship has been shown experimentally for several host–parasite systems such as myxomatosis in rabbits (Dwyer *et al.*, 1990), a protozoan parasite of monarch butterflies (de Roode *et al.*, 2008), the cauliflower mosaic virus (Doumayrou *et al.*, 2013) and HIV in humans (Fraser *et al.*, 2007). As resistance/tolerance heterogeneity between males and females has been shown in HIV (Table 1) and as our epidemiological model is consistent with that of this virus, we use this trade-off relationship to parameterize our model (see Shirreff *et al.* (2011) and Appendix A.1 in Supporting Information for further details).

To model sex-specific heterogeneity, we divide each class into males (whose total density is denoted  $N_M$ ), which can be susceptible ( $S_M$ ) or infected ( $I_M$ ) and do the same for females ( $N_F$ ,  $S_F$ ,  $I_F$ ). The structure of the model is shown in Fig. 1. Because each sex is modelled explicitly, we need to introduce a parameter  $\sigma$ ,



**Fig. 1** Structure of the epidemiological model as a function of the transmission pattern ( $h$ ). The plain lines indicate transition between states (births, infections or deaths). If  $h = 0$  (blue dashed arrows on the side), transmission is only within a sex. If  $h = 0.5$  (red dotted arrows in the middle), transmission is random. Finally, if  $h = 1$  (black dashed arrows in the middle), transmission is only from one sex to the other, which corresponds to an STI spreading in a heterosexual population.

which is the proportion of newborns that are males. We also incorporate sex-specific intrinsic mortalities  $\mu_M$  and  $\mu_F$ , here assumed to be equal. The virulence ( $\alpha$ ), which is assumed to be a parasite trait, is now expressed differently in males and females, and this is captured by the weighting terms  $A_F$  and  $A_M$ . Similarly, transmission rate is weighted depending on the route of transmission, that is male to male ( $b_{MM}$ ), female to male ( $b_{FM}$ ), male to female ( $b_{MF}$ ) and female to female ( $b_{FF}$ ). We assume that resistance reduces the parasite's growth, hence reducing both virulence ( $A_F, A_M$ ) and transmission ( $b_{FF}, b_{FM}, b_{MF}, b_{MM}$ ) factors, while tolerance only affects virulence (see Varying Resistance, Tolerance and Heterogeneity). Finally, as we assume a constant population size, we have  $\varphi(S_M, S_F, I_M, I_F) = \mu_M N_M + \mu_F N_F + A_F \alpha I_F + A_M \alpha I_M$ . The equations capturing the dynamics of the densities of susceptible and infected hosts of each sex are as follows:

$$\frac{dS_M}{dt} = \sigma \varphi(S_M, S_F, I_M, I_F) - \beta(\alpha) S_M (b_{MM} I_M + b_{FM} I_F) - \mu_M S_M \quad (2a)$$

$$\frac{dI_M}{dt} = \beta(\alpha) S_M (b_{MM} I_M + b_{FM} I_F) - (\mu_M + A_M \alpha) I_M \quad (2b)$$

$$\frac{dS_F}{dt} = (1 - \sigma) \varphi(S_M, S_F, I_M, I_F) - \beta(\alpha) S_F (b_{MF} I_M + b_{FF} I_F) - \mu_F S_F \quad (2c)$$

$$\frac{dI_F}{dt} = \beta(\alpha) S_F (b_{MF} I_M + b_{FF} I_F) - (\mu_F + A_F \alpha) I_F \quad (2d)$$

First, to understand the main effects of all the factors of the model, we make the simplifying assumption that the sex ratio in the population is constant and therefore that the population size of each of the males and the females is constant ( $N_M = N_F = 1$ ). In this case, only two equations are needed (eqn 2b and 2d) to track changes in the number of infected males ( $I_M$ ) and females ( $I_F$ ). Assuming a constant population size of each sex has the advantage of allowing us to consider diseases with either frequency-dependent or density-

variation in proportion of male births ( $\sigma$ ) on the epidemiology of the system.

This two-host general framework is similar to that described by Osnas & Dobson (2011) in which a parasite can be transmitted between hosts heterogeneous with respect to virulence  $\alpha$ . Unlike our framework, they found no effect of varying the transmission rate  $\beta$  (or 'infectivity') between parasite strains of different virulence, and so keep it constant. In our framework, we explicitly link virulence and transmission given that resistance acts on both features, while tolerance is assumed to act only on virulence and not directly on parasite transmission. Another key difference is that we incorporate heterogeneity within each host type, for example sex, using modifiers of transmission and virulence (Table S1, Supporting Information) to adjust the effects of resistance and tolerance on parasite virulence. In contrast, Osnas & Dobson (2011) do not explicitly distinguish between these aspects of immunity.

### Parasite fitness

Resistance and tolerance, in their effects on parasite load and damage, respectively, affect parasite evolution through different mechanisms. As described in the next section, we use two sets of equations for virulence and transmission to expand upon their previous introduction as single-value parameters. This allows us to model the effects of resistance, tolerance and the level of dimorphism in each.

Using equation system 2, we test the ability of a mutant parasite strain with a slightly different virulence ( $\alpha'$ ) to successfully outcompete the resident strain for susceptible hosts. For this, we need to evaluate the fitness ( $R$ ) of the mutant parasite, which can be derived from the general evolutionary epidemiology framework developed by Gandon (2004). Detailed calculations are shown in online Appendix A.2 in Supporting Information, but for a general case, we find that

$$R = \frac{\beta(\alpha')}{2\mathbf{M}\mathbf{F}} \left( b_{FF}\mathbf{M}\tilde{S}_F + b_{MM}\mathbf{F}\tilde{S}_M + \sqrt{(b_{FF}\mathbf{M}\tilde{S}_F + b_{MM}\mathbf{F}\tilde{S}_M)^2 + 4\mathbf{M}\mathbf{F}\tilde{S}_F\tilde{S}_M(b_{FM}b_{MF} - b_{MM}b_{FF})} \right) \quad (3)$$

dependent transmission, that is sexually vs. directly transmitted diseases.

We then allow the sex ratio of the population to vary, while keeping only the total host population constant (i.e.  $N = N_M + N_F$ ). This requires tracking an additional population size variable (e.g.  $S_M$ ). In addition to following changes in the proportions infected hosts of each sex, we can also study the effect of rapid

where  $\tilde{S}_F$  and  $\tilde{S}_M$  are the equilibrium densities of females and males, respectively;  $\mathbf{M} = \mu_M + A_M \alpha'$  and  $\mathbf{F} = \mu_F + A_F \alpha'$  is the rate at which an infection caused by the mutant strain ends in males and in females, respectively;  $\beta(\alpha')$  is the mutant transmission rate, and  $b_{AB}$  indicates the propensity of the parasite to be transmitted from a host of type  $A$  to a host of type  $B$ .

In some special cases, the expression of  $R$  is simpler. If there is no transmission of the parasite from one sex to the other ( $b_{FM} = b_{MF} = 0$ ), then

$$R^F = \frac{b_{FF}\beta(\alpha')}{\mathbf{F}}\tilde{S}_F \text{ or } R^M = \frac{b_{MM}\beta(\alpha')}{\mathbf{M}}\tilde{S}_M \quad (4)$$

This makes sense: if there is no contact between sexes, parasites in each sex-specific population are independent, and all that matters is their fitness in the population where they are. This aspect is particularly relevant when sex ratio within the host population varies: if one of the sexes becomes too rare, the parasite can shift to the other sex.

When transmission is solely between sexes ( $b_{FF} = b_{MM} = 0$ ), parasite fitness is determined by transmission between susceptible individuals of both sexes:

$$R = \beta(\alpha')\sqrt{\frac{b_{FM}\tilde{S}_M}{\mathbf{M}}\frac{b_{MF}\tilde{S}_F}{\mathbf{F}}} \quad (5)$$

Here, the sex ratio of the population should matter less because all the host densities are multiplied. Note that this expression is similar to that found for vector-borne pathogens that need to alternate between host types (Anderson & May, 1991).

### Varying resistance, tolerance and heterogeneity

Our goal is to study the effect of the type and intensity of host heterogeneity. We introduce four parameters to capture, respectively, the intensity of host resistance ( $\rho$ ), the intensity of host tolerance ( $\tau$ ), the heterogeneity in resistance among the sexes ( $y$ ) and the heterogeneity in tolerance among the sexes ( $z$ ). This allows us to vary only the amount of heterogeneity ( $y$  or  $z$ ), while investigating whether the intensity of the resistance or tolerance matters. Furthermore, this is also a way to compare our model to previous models without heterogeneity (by setting  $y$  and  $z$  to zero and varying  $\rho$  and  $\tau$ ).

Virulence, which we express in the model through host disease-induced mortality and include in the terms  $\mathbf{M}$  and  $\mathbf{F}$  above, is influenced by both resistance and tolerance. Importantly, we have to distinguish here between the 'intrinsic' virulence of a parasite strain (denoted  $\alpha$ ) and the virulence that is expressed in males or in females. The latter can be expressed by scaling  $\alpha$  with a parameter corresponding to the host type ( $A_F$  for females and  $A_M$  for males). Differences in resistance and tolerance between sexes should occur in  $A_F$  and  $A_M$  but not in  $\alpha$  (unless the expression of parasite traits is plastic and depends on the host type). They can be captured with the following two equations:

$$A_M = (1 - (0.5 - y)\rho)(1 - (0.5 - z)\tau) \quad (6a)$$

$$A_F = (1 - (0.5 + y)\rho)(1 - (0.5 + z)\tau) \quad (6b)$$

In system 6, we multiply the value of resistance  $\rho$  (limitation of parasite growth and blockage of transmission to the next host) by a term incorporating the resistance heterogeneity parameter  $y$ . We do the same for tolerance  $\tau$  with respective heterogeneity  $z$ . We incorporate dimorphism in such a way that it affects the sexes symmetrically in opposite directions ( $0.5 - y$  and  $0.5 - z$  in males,  $0.5 + y$  and  $0.5 + z$  in females). Resistance and tolerance ( $\rho$  and  $\tau$ , respectively) are both in  $[0, 1]$ , with the result that  $A_M$  and  $A_F$  are also constrained to  $[0, 1]$ . As  $y$  or  $z$  increases from 0, males become less resistant or tolerant, respectively, while females become more resistant or tolerant, respectively.

While tolerance does not directly affect transmission, resistance decreases both virulence and transmission due to its limiting effects on parasite growth. As for virulence, we have to distinguish between the 'intrinsic' parasite transmission rate ( $\beta$ ) and the transmission rate that is actually expressed. To this end, as shown in the expressions for  $R_0$ , we always weight  $\beta$  by scaling terms  $b_{AB}$  depending on which type of host is infecting which type. To investigate how different transmission patterns influence parasite evolution, we model transmission using four equations similar to those for virulence. Of the four equations, two are for transmission within sexes and two for transmission between sexes:

$$b_{MM} = (1 - h)(1 - (0.5 - y)\rho) \quad (7a)$$

$$b_{FM} = h(1 - (0.5 + y)\rho) \quad (7b)$$

$$b_{MF} = h(1 - (0.5 - y)\rho) \quad (7c)$$

$$b_{FF} = (1 - h)(1 - (0.5 + y)\rho) \quad (7d)$$

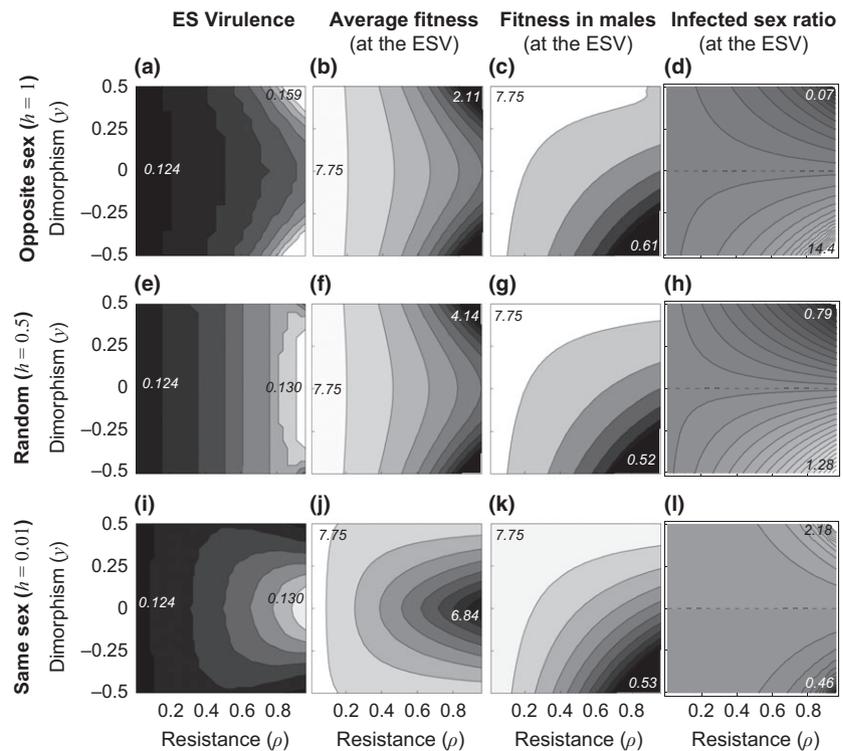
Note that variations in the parameter  $h$  allow us to study the continuum of situations ranging from no transmission between host sexes ( $h = 0$ ) to only transmission between host sexes ( $h = 1$ ). When  $h = 0.5$ , there is no bias in transmission.

## Results

### Resistance ( $\rho$ ) and resistance dimorphism ( $y$ )

As expected, increasing the average level of host resistance ( $\rho$ ), that is moving horizontally on Fig. 2a,e,i, increases the evolutionarily stable level of virulence (ESV) towards which the parasite population converges. Importantly, this virulence ( $\alpha$ ) is the 'intrinsic' virulence of the pathogen, and it may differ from the 'expressed' virulence (which depends on the type of host, male or female, the parasite infects).

The effect of dimorphism between the sexes is less straightforward and depends on the level of resistance



**Fig. 2** Effect of resistance ( $x$ -axis,  $\rho$ ) and its dimorphism ( $y$ -axis,  $y$ ) on parasite epidemiology and evolution. For different transmission patterns between hosts ( $h$ ), we show effects on the evolutionary stable virulence (ESV, panels a, e and i), parasite average fitness (panels b, f and j), parasite fitness in males (panels c, g and k) and sex ratio in the infected population, that is the density of infected males divided by the density of infected females (panels d, h and l). The numerical values on each plot indicate the minima and maxima. Other parameter values are default as given in Table S1.

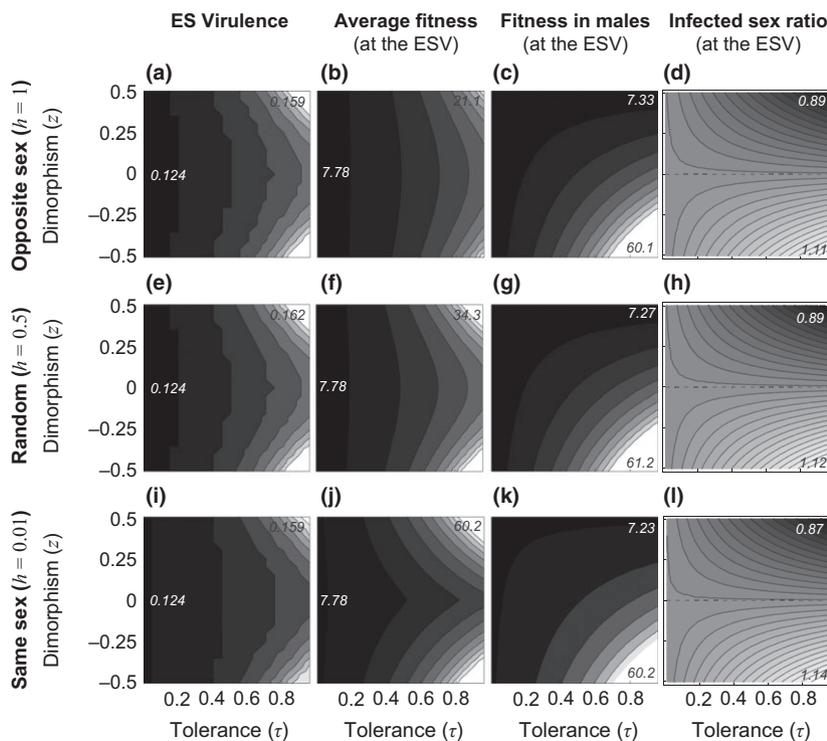
of the host population. When resistance ( $\rho$ ) is low, increasing dimorphism in resistance ( $y$ ) has very little effect on the ESV (the left part of Fig. 2a,e,i). When  $\rho$  is high, sex heterogeneity matters, but the effect depends on the contact structure between the sexes. If transmission is only between hosts of opposite sex ( $h = 1$ ), increasing  $y$  increases the ESV (right hand side of Fig. 2a). This occurs because the parasite always has to go through the most resistant sex. If the transmission is random,  $y$  has little effect even for high  $\rho$ . In this case, by chance the parasite can infect hosts that are less resistant. However, if transmission tends to occur between individuals of the same sex, increased dimorphism selects for lower ESV (Fig. 2i). This is because, as shown above, the parasite spreads almost exclusively in the sex where its fitness ( $R$ ) is maximized (Fig. 2k,l). Here, this will be the less resistant sex, which will lead to a lower ESV.

If we consider the parasite fitness at the ESV, we find that for transmission between different sexes (Fig. 2a) or between the same sex (Fig. 2j), a higher ESV corresponds to a lower parasite fitness ( $R$ ). This is not the case if the transmission pattern is random because the lowest fitness is reached for high resistance and high dimorphism, whereas the highest ESV is reached for high resistance and low dimorphism (Fig. 2f). This can be understood by remembering that our assumptions on resistance and tolerance are made such that the average level of resistance/tolerance in

the host population is constant. In other words, in a case without dimorphism, the expressed virulence is multiplied by  $(1-0.5\rho)(1-0.5\tau)$  both for males and for females, and in a case with extreme dimorphism, it is multiplied by 1 and  $(1-\rho)(1-\tau)$ . Therefore, allowing for high dimorphism allows super-resistant (or super-tolerant) hosts to exist. This is why fitness decreases with increased heterogeneity in panels b and f of Fig. 2.

The fitness in males achieved by a parasite strain with an ESV does not depend strongly on the transmission pattern, and the lowest parasite fitness is achieved when males are most resistant (Fig. 2c,g,k). Note that in the latter case (bottom right corner), the expression of the fitness is smaller than 1, suggesting that the parasite cannot persist in males and that nonresistant hosts serve as an effective reservoir. As we did not assume any difference between sexes other than resistance and tolerance in the epidemiological model, the pattern for female fitness is the symmetric opposite to that of males (figures not shown).

Finally, if we consider the sex ratio of the infected hosts at the ESV, that is the ratio  $\tilde{I}_M/\tilde{I}_F$ , we see a strong effect of the transmission pattern. If there is transmission between the sexes, the higher the resistance, the more we see a bias in the sex ratio such that the most resistant sex is more frequently infected (Fig. 2d,h). This is likely due to the high ESV and the alternation of host sexes: individuals from the resistant sex die



**Fig. 3** Effect of tolerance ( $x$ -axis,  $\tau$ ) and its dimorphism ( $y$ -axis,  $z$ ) on parasite epidemiology and evolution. See Fig. 2 for further details.

rapidly from the infection and are less present at equilibrium. If transmission is almost exclusively between individuals of the same sex, however, we find that the less resistant sex is the most infected (Fig. 2l). This is because the parasite cannot persist in the most resistant sex.

### Tolerance ( $\tau$ ) and tolerance dimorphism ( $z$ )

In general, increased tolerance ( $\tau$ ) increases the ESV more gradually than resistance does, but the most striking difference is that the variation pattern is largely unaffected by variation in contact patterns between the sexes (Fig. 3a,e,i). This occurs because in a tolerant host, parasites can increase transmission without incurring an additional cost in virulence, such as would occur in a resistant host.

As for resistance, sexual dimorphism has no effect if  $\tau$  is low. If  $\tau$  is high, increasing dimorphism increases virulence. Contrary to resistance, these increases in virulence always correlate with increases in parasite fitness (Fig. 3b,f,j).

Overall, the most striking pattern is that in the case of tolerance, the highest parasite virulence (and fitness at the ESV) is always achieved when there is strong dimorphism. As mentioned above in the case of resistance, this can be understood by bearing in mind that allowing for high dimorphism allows super-tolerant hosts to exist. This leads to high parasite fitness in one of the sexes, as illustrated by the steep fitness

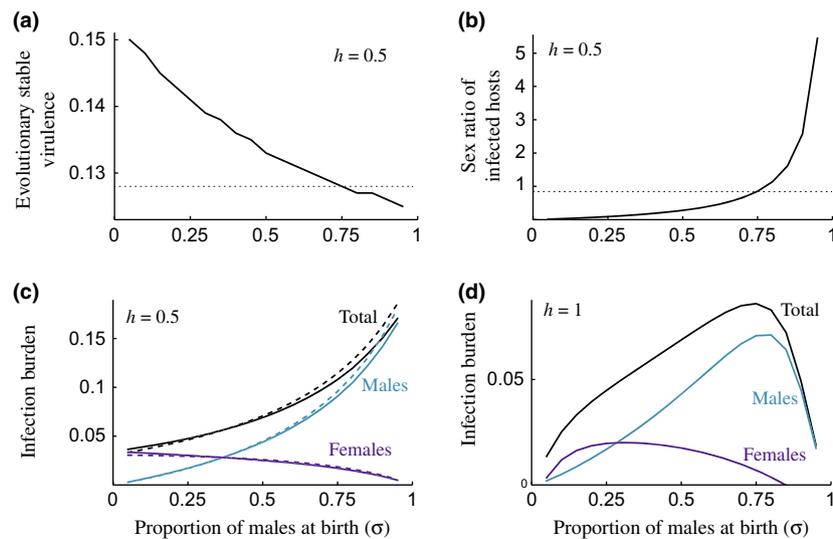
landscapes in the third column in Fig. 3. Note that in this case, we do not observe parasite extinction in any of the sexes.

Finally, we observe less pronounced differences in sex ratio in the population of infected hosts than for the resistance case, which makes sense as there is little host mortality with high tolerance (Fig. 3d,h,l). Furthermore, the sex ratio in infected hosts is always biased in favour of the more tolerant sex.

### Varying the proportion of males at birth ( $\sigma$ )

We have assumed so far that the proportion of each sex in the host population was fixed to 0.5. This is oversimplifying because the infection can bias the sex ratio in the host population but also because the host sex ratio at birth can be biased. In this subsection, we allow for the population sex ratio to vary.

To restrict the parameter space, we set resistance ( $\rho = 0.95$ ) and resistance heterogeneity ( $\gamma = 0.4$ ) to high values and study how the proportion of males at birth ( $\sigma$ ) affects three variables: the ESV, the ratio of infected males to infected females and finally the burden caused by the parasite on the host population, that is the number of deaths per unit of time due to the infection (e.g. for males  $A_M \bar{a}_M$ ). For the latter case, we compare two scenarios: one where the parasite is always adapted to a nonbiased proportion of males at birth ( $\sigma$ ) and one where the parasite is adapted to  $\sigma$ . The first case is intended to capture a situation where  $\sigma$



**Fig. 4** Effect of changing of the proportion of males at birth ( $\sigma$ ) on ESV (a), sex ratio of infected hosts (b) and infection burden (c and d). Parameter values are default and  $\tau = 0.95$  and  $z = 0.4$ . In panels a, b and c, transmission pattern between sexes is random ( $h = 0.5$ ), but in panel d, transmission is only between different sexes ( $h = 1$ ). Dashed horizontal lines in panels a and b indicate the value obtained in a model with constant sex ratio in the host population. In panel c, total infection burden in males is shown in blue, females in purple, and overall population in black. The dashed lines correspond to the case where the parasite is adapted to a value of  $\sigma$  of 0.5, and the solid lines indicate infection loads when the parasite evolves rapidly and adapts the ESV dictated by the strength of host tolerance and the proportion of males at birth.

would be adjusted rapidly, for example in a plastic way, to fight the infection. The second case predicts how parasites would react to this sex ratio adjustment.

As expected, biasing the sex ratio in favour of the most resistant sex selects for higher levels of virulence (Fig. 4a). Interestingly, if the sex ratio at birth is unbiased ( $\sigma = 0.5$ ), the ESV is still moderately higher than in our previous model (dashed line in Fig. 4a) with constant population sex ratio. This is due to feedbacks in the population dynamics, which are materialized by a strongly biased sex ratio among infected hosts at the equilibrium with much fewer infections in the less resistant sex (Fig. 4b). We find qualitatively similar results when varying tolerance instead of resistance or when  $h$  is set to 0.01 (results not shown).

When considering the burden caused by the parasite on the host population, we see that biasing  $\sigma$  in favour of the most resistant sex yields a decrease in infection burden (Fig. 4c). This means that most individuals dying are those from the resistant sex. If we consider the scenario where the parasite population is adapted to an unbiased sex ratio at birth (i.e.  $\sigma = 0.5$ , dashed curves in Fig. 4c), biasing this sex ratio in favour of the most resistant host yields a stronger decrease in infection burden. As expected, allowing parasite virulence to evolve in response to this change increases infection burden. However, from a host perspective, the total decrease in infection burden is still worth the adjustment in  $\sigma$ . If transmission occurs between individuals

of the same sex ( $h = 0.01$ ) we find similar patterns (not shown).

When transmission is only between sexes ( $h = 1$ ), we see qualitative changes in the results. First, we find that the ESV is constant (figure not shown). This makes sense as the parasite always has to alternate between host sexes so the population sex ratio does not matter. We also see a change in the infection burden because strongly biasing the sex ratio in favour of the less resistant sex eventually leads to a decrease in infection burden (Fig. 4d). Even though the total population size is constant, the male and female population sizes are allowed to vary, and since when  $h = 1$  transmission can only be from one sex to the other, we observe an effect of the density-dependent transmission assumption of our model. In other words, the combination of a strong decrease in the total density of females and their high resistance to the disease leads to a strong decrease in the force of infection of the parasite. When we assume frequency-dependent transmission, which is more appropriate for a case where  $h = 1$  because it is likely to behave as a sexually transmitted infection (STI), we find results similar to the case where  $h = 0.5$ .

## Discussion

Independently of behavioural differences, which can alter infection rates and severity (Zuk & McKean, 1996), sex-specific immune responses to infection are

documented in all classes of infection, including viral, bacterial, fungal and macroparasitic (Table 1). We developed a mathematical model to investigate how immune dimorphism and variation in levels of contact between hosts affect parasite virulence evolution. We found that increases in either resistance or tolerance select for more virulent parasites under most conditions. However, these patterns are strongly affected by the level of dimorphism, patterns of contact (between and within sexes) and variation in the strength of transmission between hosts.

Note that the level of detail of Table 1 is limited because the mechanisms of resistance and tolerance are often not clearly defined, and we caution against stringent interpretations of the presence, absence or levels of particular elements, for example CD4<sup>+</sup> cells and interleukins, as clear indicators for either type of immune response. Here, for resistance, we only considered those studies that specifically provided evidence for either a clear and direct response against a pathogen (such as antibiotic or antiviral response) coupled with decreased and/or delayed mortality, and/or reduced disease severity. Conversely, we evaluated an anti-inflammatory response as being more consistent with tolerance, coupled with increased survivability or longevity, or decreased severity of infection in conjunction with an equivalent or higher parasite load. In realistic conditions, host immunity is a combination of tolerance and resistance mechanisms (Boots & Bowers, 1999; Restif & Koella, 2004; Råberg *et al.*, 2007; Boots *et al.*, 2009; Råberg *et al.*, 2009; Lefèvre *et al.*, 2011; Ayres & Schneider, 2012). Nevertheless, simplifying the tremendous complexity of immune responses by means of distinguishing between tolerance and resistance has become increasingly popular because it provides biologists with a simple way to detect biologically meaningful host differences (Råberg *et al.*, 2007). These definitions, although debatable, are consistent within the current literature, and further discussion on the topic can be found in genetic studies by Råberg *et al.* (2007) and in reviews (Schneider & Ayres, 2008; Ayres & Schneider, 2012).

### Effects of resistance, tolerance and dimorphism

The degree to which an individual host resists or tolerates infection by a parasite is a key determinant of both the evolutionary stable virulence (ESV) and the parasite fitness. In hosts that have a strong response to infection, either through resistance or through tolerance, a parasite may attain higher fitness by adopting a more virulent strategy and concurrently higher transmission. When dimorphism is high, this aggressive strategy is maladaptive in more sensitive hosts, resulting in decreased overall parasite fitness. In fact, for very high dimorphism combined with high resistance, the most adapted parasite strain kills the nonresistant host so rapidly that it is main-

tained only in the resistant host. This finding is in agreement with conclusions by Gandon (2004) that the ESV strongly depends on the growth rate in, or reproductive value of, each host type.

Regoes *et al.* (2000) also explored virulence evolution in a two-host system, using a large number of parasite strains differing in reproductive growth but not infectivity. They show that when specialist strains are favoured, heterogeneity is insufficient on its own to mediate virulence evolution, leading to escalation in the more valuable host. We discuss the role of such epidemiological effects below with respect to sex ratio.

### The case of HIV

The questions described in this work seem particularly relevant with respect to HIV, for which marked differences for males and females have been documented for viral load (Donnelly *et al.*, 2005; Prins *et al.*, 2005; Hollingsworth *et al.*, 2008); patterns of immune response and viral load over the course of infection (Donnelly *et al.*, 2005); transmission (Boily *et al.*, 2009); and responses to treatment and clinical outcomes for comparable viral loads (Nicastri *et al.*, 2005). These data suggest that males and females have different responses to the virus, with potentially different viral dynamics (McClelland & Smith, 2011). As shown in Table 1 and in Appendix A.1 (Supporting Information), we can interpret the observed differences between sexes by saying that females are more resistant than males to HIV (they tend to have lower viral loads) and that males are more tolerant than females (even though they have a higher viral load than females, their virulence is the same). However, a precise parameterization is complicated because the difference between males and females only informs us on the heterogeneity parameters ( $y \approx 0.15$  and  $z \approx -0.15$ ) but not on the magnitude of the resistance and tolerance ( $\rho$  and  $\tau$ ).

One possibility to exploit this data would be to compare population with different transmission patterns, for example heterosexuals vs. men having sex with men (MSM), which have been shown to lead to separate epidemics, in Switzerland for instance (Kouyos *et al.*, 2010). The effect of tolerance does not seem to be affected by the transmission pattern  $h$ , but this is not the case for resistance, and we would expect to find slightly higher virulences with heterosexual transmission ( $h \approx 1$ ) than with homosexual transmission ( $h \approx 0$ ). Also, the higher the proportion of heterosexual transmission, the more there should be a bias in the sex of infected hosts, with females being more infected.

Of course, these results are very speculative. First, numerous other factors affect the selective pressure on parasite evolution. For instance, transmission rates from males to females and from females to males are

not equal (Boily *et al.*, 2009). Furthermore, the transmission network itself is likely to be complicated, with strong host heterogeneity in terms of the number of partners (Anderson & May, 1991). As network topology is known to affect virulence evolution (van Baalen, 2002), capturing all these details with a single parameter ( $h$ ) is likely to be too oversimplifying to draw results applicable to HIV. Second, a recent study that tried to disentangle resistance from tolerance in HIV infections found no differences between host sexes (Regoes *et al.*, 2014). Finally, in our model, we did not vary resistance and tolerance simultaneously. This is because we already needed two parameters to carefully assess the role of resistance or of tolerance. One possibility to vary both parameters, while keeping the total number of parameters reasonable, would be to assume a trade-off relationship such that being more resistant implies being less tolerant. However, although there is some evidence supporting such a trade-off (Råberg *et al.*, 2007), further work would be needed to ascertain the shape of this relationship.

### Sex ratio

Parasite evolution is likely to be strongly linked to the host population sex ratio as increasing the proportion of the most resistant/tolerant sex will have similar consequences to an increase in the average level of host resistance/tolerance. There are also less direct effects. For instance, differences in male and female mortality will shape the population sex ratio, which itself will affect parasite evolution. Note that variations in the host population sex ratio can be the result of the infection, but can also be caused by a biased sex ratio at birth in the host population. In fact, we find that varying the sex ratio at birth might be an adaptive strategy for hosts to minimize disease burden.

When allowing the host population's sex ratio to vary, we see that even if the sex ratio at birth is unbiased, the ratio of infected males to infected females is much more biased than what is predicted in a population with constant sex ratio. This corresponds to a higher ESV than what is predicted with the constant sex ratio model. Variations in population sex ratio thus amplify the evolutionary consequences of host sex heterogeneity on parasite evolution.

We also show that variations in the proportion of males at birth have pronounced effects on virulence evolution and the sex ratio of the infected population. As we hypothesized, this variation can decrease the infection burden on the host population. In response to these biased sex ratios, parasites can evolve higher virulences, but this adaptation has only a negligible influence on the total host mortality due to the parasite. Therefore, we suggest that it would be worthwhile to further study biases in sex ratio in combination with sex heterogeneity in resistance/tolerance.

### Perspectives

We built a generic model to explore different types of sex-based heterogeneity in immunity; an obvious development for future work would be to build a sex-specific model that incorporates more complex population dynamics. This would allow a more careful investigation of the evolution of parasite specialization to host sexes. In a recent essay, Duneau & Ebert (2012) argue such an evolutionary branching in the parasite population, that is the transition from a monomorphic to a dimorphic population, should be observable for a wide range of values. However, their results are based on a verbal model, which is not satisfying. One problem in addressing the question of evolutionary branching is that it strongly depends on population dynamics feedbacks: a model with density-dependent transmission by Gandon (2004) did find branching, whereas a model with frequency-dependent transmission did not find it (Osnas & Dobson, 2011). Here, as shown in Appendix B (Supporting Information), we also never find branching (even for very low values of  $h$ ), which is consistent with our assumption of constant population size. Determining the range of parameters from the host population dynamics that lead to branching would allow us to test the generality of the claim made by Duneau & Ebert (2012).

Some studies suggest that coevolution between the host response and parasite transmission should increase the likelihood of evolutionary divergence (Best *et al.*, 2010). Incorporating coevolutionary dynamics would provide a more accurate picture of how parasites are able to adapt to sexually dimorphic host responses and how hosts may respond to parasites that specialize to one host sex or the other. Accounting for within-host evolution of parasites would improve our understanding of how delays in transmission and time spent in a particular host with a specific immune response can influence the likelihood of divergence, persistence of strains and potential coexistence. We did not investigate interactions between sexual dimorphism in immune response and intrinsic mortality. Relationships between lifespan and body size are common. Sexual dimorphism in body size, behaviour and other physiological characteristics can thus have consequences for both disease epidemiology (de Leo & Dobson, 1996) and parasite evolution (Anderson & May, 1982; Frank, 1996). Williams (2012) shows that in heterogeneous host populations, increases in the intrinsic mortality of the host can reduce the evolutionarily stable virulence, in contrast to an increasing level of host recovery rate, which tends to increase it. It would be worthwhile to test these hypotheses in experimental populations, for instance by manipulating intrinsic survival through limiting reproduction, increasing resource availability or otherwise artificially manipulating the intrinsic mortality in one sex.

Finally, there is currently a shortage of experimental treatments on these issues, and empirical evidence for sex-specific evolution of parasites is limited (but see Lee *et al.*, 2013). Experimental evolution approaches (see Masri *et al.*, 2013, on a related topic) may provide opportunities to demonstrate these differences, as they allow to separate evolution of a parasite in one of the sexes or even to control the sex ratio of the host population. By framing the multihost parasite evolution theory in terms of dimorphism in tolerance and resistance between host sexes, we support a deeper examination of host-based, sex-specific variation in observed pathology and susceptibility for many diseases. Combining theoretical and empirical knowledge on this issue is a necessary step to allow us to be one step ahead of parasites and develop 'evolution-proof' antiparasite strategies, while potentially decreasing the morbidity of many such diseases.

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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Appendix A** Supplementary methods.

**Appendix B** Supplementary results.

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