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What Does Tolerance Mean for Animal Disease Dynamics When Pathology Enhances Transmission?

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Abstract

Host competence, or how well an individual transmits pathogens, varies substantially within and among animal populations. As this variation can alter the course of epidemics and epizootics, revealing its underlying causes will help predict and control the spread of disease. One host trait that could drive heterogeneity in competence is host tolerance, which minimizes fitness losses during infection without decreasing pathogen load. In many cases, tolerance should increase competence by extending infectious periods and enabling behaviors that facilitate contact among hosts. However, we argue that the links between tolerance and competence are more varied. Specifically, the different physiological and behavioral mechanisms by which hosts achieve tolerance should have a range of effects on competence, enhancing the ability to transmit pathogens in some circumstances and impeding it in others. Because tissue-based pathology (damage) that reduces host fitness is often critical for pathogen transmission, we focus on two mechanisms that can underlie tolerance at the tissue level: damage-avoidance and damage-repair. As damage-avoidance reduces transmission-enhancing pathology, this mechanism is likely to decrease host competence and pathogen transmission. In contrast, damage-repair does not prevent transmission-relevant pathology from occurring. Rather, damage-repair provides new, healthy tissues that pathogens can exploit, likely extending the infectious period and increasing host competence. We explore these concepts through graphical models and present three disease systems in which damage-avoidance and damage-repair alter host competence in the predicted directions. Finally, we suggest that by incorporating these links, future theoretical studies could provide new insights into infectious disease dynamics and host-pathogen coevolution.

Keywords

Disease Ecology, Ecoimmunology, Parasites, Pathogens, Host Competence

Disciplines

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What Does Tolerance Mean for Animal Disease Dynamics When Pathology Enhances Transmission?

Running Title: Tolerance, pathology, and transmission

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Abstract

Host competence, or how well an individual transmits pathogens, varies substantially within and among animal populations. As this variation can alter the course of epidemics and epizootics, revealing its underlying causes will help predict and control the spread of disease. One host trait that could drive heterogeneity in competence is host tolerance, which minimizes fitness losses during infection without decreasing pathogen load. In many cases, tolerance should increase competence by extending infectious periods and enabling behaviors that facilitate contact among hosts. However, we argue that the links between tolerance and competence are more varied. Specifically, the different physiological and behavioral mechanisms by which hosts achieve tolerance should have a range of effects on competence, enhancing the ability to transmit pathogens in some circumstances and impeding it in others. Because tissue-based pathology (damage) that reduces host fitness is often critical for pathogen transmission, we focus on two mechanisms that can underlie tolerance at the tissue level: damage-avoidance and damage-repair. As damage-avoidance reduces transmission-enhancing pathology, this mechanism is likely to decrease host competence and pathogen transmission. In contrast, damage-repair does not prevent transmission-relevant pathology from occurring. Rather, damage-repair provides new, healthy tissues that pathogens can exploit, likely extending the infectious period and increasing host competence. We explore these concepts through graphical models and present three disease systems in which damage-avoidance and damage-repair alter host competence in the predicted directions. Finally, we suggest that by incorporating these links, future theoretical studies could provide new insights into infectious disease dynamics and host-pathogen coevolution.

Introduction

The ability to effectively transmit pathogens, also known as host competence, varies dramatically among individual animals (Gervasi et al. 2015, Martin et al. 2016, Martin et al. 2019, Burgan et al. 2019). Because such heterogeneity can alter the course of epidemics and epizootics (e.g., Llyod-Smith et al. 2005, Hall *submitted for publication—this issue*), revealing the host traits underlying this variation is critical to understanding and predicting infectious disease dynamics. Two key drivers of variation in competence are host resistance, or the ability to kill invading pathogens, and host tolerance, or the ability to maintain fitness during infection without reducing pathogen numbers (Simms 2000, Medzhitov et al. 2012, Råberg 2014, Gervasi et al. 2015, Martin et al. 2016, Martin et al. 2019, Burgan et al. 2019). Resistance will impact competence in at least two predictable ways: reducing the amount of pathogen available for transmission at any given instant and limiting the duration of infection. In contrast, we know less about how tolerance will impact competence in animals (Martin et al. 2016, Adelman and Hawley 2017, Burgan et al. 2019, Martin et al. 2019). Prior work has suggested that because tolerant animals can harbor high pathogen loads while avoiding death and maintaining fitness-enhancing behaviors, these hosts may be particularly likely to both contact and pass pathogens to susceptible individuals (Martin et al. 2016, Adelman and Hawley 2017, Burgan et al. 2019, Martin et al. 2019). However, different physiological and behavioral mechanisms that facilitate tolerance are likely to impact transmission in varied, even opposite ways (Adelman and Hawley 2017, Burgan et al. 2019). By extension, because transmission directly enhances pathogen fitness, tolerance is also likely to affect the evolution of pathogen virulence and host-pathogen coevolution in varied ways. Here, we explore the transmission consequences of different physiological mechanisms of tolerance, as well as their implications for co-evolution, focusing

on a common subset of infectious diseases: those in which pathology, or tissue damage during infection, enhances pathogen transmission (see Table S6 in Leggett et al. 2017).

Such links between pathology and transmission are especially relevant to studying tolerance and competence in animals because pathology is frequently used as a proxy for fitness reductions in animal systems (reviewed in Burgan et al. 2019). Specifically, because fitness can be difficult or impossible to quantify in many animals, studies often define animal tolerance using a regression of the severity of a given type of pathology, such as weight loss or anemia, versus pathogen load, with more tolerant phenotypes showing shallower slopes (Burgan et al. 2019). We recently termed such metrics "tissue-specific tolerance"—essentially the ability to maintain somatic function despite a given pathogen load (Adelman and Hawley 2017). Alternatively, decreases in fitness-enhancing behaviors during infection could be used as a proxy for host fitness reductions, generating a metric we have termed "behavioral tolerance" (Adelman and Hawley 2017, Burgan et al. 2019). Burgan and colleagues (2019) showed that the specific behaviors underlying behavioral tolerance can have very different implications for host competence. Similarly, we argue that the different physiological mechanisms by which hosts reduce tissue pathology will determine whether tissue-specific tolerance enhances or diminishes host competence.

Although the precise links between tissue pathology and transmission vary across diseases, such pathology often facilitates transmission. For example, the release of replicated intracellular pathogens through cell lysis, such as red blood cell bursting during malarial infections, is necessary for pathogen transmission and also damages both infected cells and surrounding host tissues (Ferreira et al. 2008, Greenwood et al. 2008). More generally, a recent review of over 60 human pathogens found that pathology (through effects on either physiology

or behavior) increased transmission in over 50% of systems, had no effect on transmission in about 30%, and inhibited transmission in only about 20% (see table S6 in Leggett et al. 2017). We note that the study by Leggett and colleagues (2017) focused on pathogen macro-evolution using comparative methods. Thus, their conclusions about virulence evolution differ from theoretical and empirical examinations of within-species co-evolutionary dynamics (Alizon et al. 2009, Leggett et al. 2017), which are more in keeping with the processes examined in this paper. Regardless of macro-evolutionary trends, if the number of diseases in which pathology enhances transmission is similarly high across all animals, reduced pathology through tissue-specific tolerance could inhibit, rather than enhance, transmission in a great many disease systems.

We are not aware of any empirical or theoretical studies that have directly tested whether tolerance can inhibit pathogen transmission by decreasing pathology nor how such links affect pathogen virulence and host-pathogen coevolution. However, Vale and colleagues (2014) explored similar ideas. Their models predicted how the prevalence and virulence of human pathogens will evolve under drug therapies that reduce the impacts of pathogen virulence factors ('anti-virulence' therapies) or limit host tissue damage ('pro-tolerance' therapies), both without reducing pathogen load. Generally, their results suggest that 'pro-tolerance' therapies can select for more virulent pathogens, as well as a higher pathogen prevalence. However, their models did not allow 'pro-tolerance' therapies to directly alter transmission efficiency. As such, both empirical and theoretical studies are needed to determine how host tolerance mechanisms that reduce transmission-relevant pathologies will alter epidemic dynamics and selection on infectious agents.

Here, we address this knowledge gap while challenging the idea that tolerance necessarily increases the transmission of pathogens. As much more is known about resistance in

animals (Råberg 2014) and because the transmission consequences of behavioral tolerance have been reviewed elsewhere recently (Adelman and Hawley 2017, Burgan et al. 2019), we concentrate on tissue-specific tolerance. Moreover, although the behavior and physiology of uninfected individuals undoubtedly alters disease dynamics (e.g., Curtis 2014, Schaller et al. 2015, Hawley et al. 2011), in the interest of space, our review centers exclusively on infected individuals. Further, we focus on systems in which pathology enhances transmission, as these may be more common than previously thought (Leggett et al. 2017, supplemental material, Table S6). In these systems, we propose that two different underlying mechanisms of tissue-specific tolerance, damage-avoidance and damage-repair (Medzhitov et al. 2012), should have opposite effects on hosts' overall transmission potential, or competence. We also discuss the co-evolutionary implications of these two mechanisms of tolerance. We then present three example systems in which different mechanisms of tissue-specific tolerance may result in either increased or decreased pathogen transmission. Within each case study, we also briefly consider how tolerance in these systems may alter pathogen virulence and host-pathogen coevolution.

A Simple Framework for Linking Tolerance and Transmission

A useful metric for exploring the impacts of tolerance on transmission is the number of new infections caused by a given infected host, also known as the individual reproductive number, V (Lloyd-Smith et al. 2005). V incorporates contact rate (the rate at which an infected host encounters susceptible individuals), infectiousness (the probability that transmission occurs given contact), and duration of the infectious period (VanderWaal and Ezenwa 2016), such that:

$$V = Contact\ rate \times Infectiousness \times Infectious\ period$$

Different mechanisms of tolerance will contribute to variation in distinct components of *V*. Behavioral tolerance will have the most impact on contact rates, with outcomes dependent on both spatial scales (local vs. regional) and transmission modes (direct vs. vector-borne), as discussed elsewhere (Adelman and Hawley 2017, Burgan et al. 2019). The impacts of tissue-specific tolerance on infectiousness and the infectious period, however, are less clear.

To explore these links, we consider two distinct, though not mutually exclusive, processes that underlie tissue-specific tolerance: damage-avoidance and damage-repair (Medzhitov et al. 2012). For example, hosts can avoid damage by down-regulating pro-inflammatory cytokines or reactive oxygen species in infections where immunopathology plays a large role in tissue damage during (Graham et al. 2005, Råberg et al. 2009, Sears et al. 2011). On the other hand, hosts can maintain tissue function by increasing the rate at which they repair cells through processes such as the unfolded protein response, which degrades misfolded or damaged proteins and upregulates chaperone protein production (Richardson et al. 2010). Alternatively, hosts may repair tissues by quickly generating new, healthy cells to replace diseased or damaged ones (Medzhitov et al. 2012). These examples are not exhaustive; many damage-avoidance and damage-repair mechanisms may play a role in tolerance and these mechanisms likely differ among hosts and diseases (Soares et al. 2014).

When pathology enhances transmission potential, we predict that tolerance via damage-avoidance vs. damage-repair will have very different consequences for *V*. To illustrate these differences, we constructed a series of graphical models that link infectiousness and the infectious period with tolerance-mediated reductions in transmission relevant pathology (Fig. 1). These models assume that 1) transmission only occurs above a given threshold in pathology, 2) these infections do not cause direct mortality in non-tolerant hosts, and 3) hosts eventually clear

these pathogens. Given these assumptions, if hosts achieve tolerance through damage-avoidance alone, tolerance reduces transmission relevant pathology, limiting infectiousness (and potentially the infectious period), resulting in a lower value of *V* (Fig. 1A,B). In contrast, if hosts achieve tolerance through damage-repair alone, the pathology that enhances transmission still occurs (Fig. 1C). Further, since damaged tissue is replaced or repaired rapidly, the pathogen has an extended opportunity to infect new tissue and continue transmitting. Thus, infectiousness peaks at the same level, but the duration of the infectious period is extended and *V* increases (Fig. 1C,D). When hosts achieve tolerance via both mechanisms, a number of scenarios are possible, including diminished infectiousness, but extended infectious periods, resulting in either increased or decreased *V* (Fig. 1E,F). We summarize these predicted outcomes and their underlying steps in Fig. 2. Below, we illustrate potential real-world examples of these predictions using three case studies that match the above conditions.

Tolerance and host-pathogen co-evolution

The potential for tissue-specific tolerance to either inhibit or enhance transmission will complicate predictions of how tolerance alters host-pathogen co-evolution (e.g., Best et al. 2014). If damage-avoidance mechanisms of tolerance decrease the intensity or duration of transmission-relevant pathology, pathogens should face intense selection pressures to cause increased pathology (virulence), ensuring transmission to naïve hosts. As virulence increases, host should, in turn, be selected to better tolerate or resist pathogens. Thus, damage-avoidance mechanisms may lead to host-pathogen evolutionary arms-races similar to those selected for by resistance mechanisms (e.g., Dybdahl and Lively 1998, Lively and Dybdahl 2000). Conversely, if damage-repair mechanisms of tolerance increase the length of the infectious period, prolonged

infections should increase the total amount of transmission. Thus, pathogens will be under less selective pressure to replicate and transmit as quickly as possible, potentially selecting for pathogens that are less virulent (Miller et al. 2006). In addition, pathogens would not be under pressure to suppress damage-repair mechanisms of tolerance, as those mechanisms would actually enhance pathogen fitness. Prolonged infectious periods would also increase pathogen prevalence within a population, which should select for damage-repair mechanisms of tolerance to go to fixation within host populations (Roy and Kirchner 2000, Miller et al. 2005). When damage-avoidance vs. damage-repair-based tolerance varies either within or between hosts, tolerance could place opposite selective pressures on pathogens. Previous co-evolutionary models suggest that heterogeneity in tolerance mechanisms (i.e., mortality vs. fecundity tolerance) may preclude the fixation of tolerance in host populations (Best et al. 2008).

Our predictions concerning increased or decreased pathogen virulence, discussed further within each of our case-studies below, only consider the direct effects of damage-avoidance and damage-repair mechanisms of tolerance on transmission. Although we make preliminary predictions here, it is important to consider that many other factors will affect the evolution of virulence (Alizon et al 2009). For example, theory suggests that the efficacy of tolerance mechanisms at different levels of pathogen replication and pathogen virulence in non-tolerant hosts can dramatically change the trajectory of virulence evolution (Miller et al., 2006). Thus, further empirical and theoretical explorations of scenarios where tolerance either enhances or impedes transmission, that also take into consideration other important factors of selection, will prove particularly fruitful.

Case Studies

Damage-Avoidance: House finches and *Mycoplasma gallisepticum*

Damage avoidance mechanisms of tolerance will allow hosts to prevent pathology before it occurs. As we predict above, when this pathology is important for pathogen transmission, tolerance through damage avoidance is likely to decrease transmission by decreasing the infectiousness of hosts (Fig. 1A,B, Fig. 2A). Pathology of mucosal tissues may be an important source of pathogen shedding (e.g., Weber and Stilianakis 2008, Adelman et al. 2013a). However, mucosal tissues are also highly susceptible to loss of function through inflammatory immunopathology (Sears et al. 2011), making such pathology a key target for damage-avoidance mechanisms. In this case study, we suggest that immunopathology within house finch (*Haemorhous mexicanus*) mucosal tissues is likely important for the transmission of *Mycoplasma gallisepticum* (MG) and that this pathology may be limited by damage-avoidance mechanisms of tolerance. We predict that a decrease in either the severity or duration of pathology in house finches infected with MG will decrease host infectiousness or infectious period, respectively, ultimately reducing individual reproductive number (V) and pathogen transmission.

Mycoplasma gallisepticum (MG) is an emerging bacterial pathogen of house finches that spilled over from domestic poultry in the mid 1990's (Dhondt et al. 1998, Hochachka et. al. 2013, Delaney et al. 2012). Since that initial spill-over, MG has spread to house finch populations across North America (Hochachka and Dhondt 2000, Ley et al. 2006, Staley et al. 2018). Transmission in this system appears to occur via fomites, particularly bird feeders, where MG can remain infective for up to 12 hours after deposition (Dhondt et al. 2007, Adelman et al. 2015).

After infection with MG, house finches develop fitness-relevant pathologies, including mild to severe conjunctivitis (Luttrell et al. 1998), which likely reduces survival in the wild through reduced predator detection (Faustino et al. 2004, Adelman et al. 2017). As in most host-pathogen systems, resistance likely reduces the efficacy of transmission, as transmission occurs most readily during the mid-point of infection, when pathogen load is highest (Dhondt et al. 2008, Hawley et al 2010). However, tissue-specific tolerance may also play a key role in transmission efficacy. Critical to the scope of this paper, finches with similar pathogen loads but more severe conjunctivitis (i.e., lower tissue-specific tolerance) deposit more pathogen onto fomites (bird feeders) than those with less severe conjunctivitis (Adelman et al. 2013a) and may transmit infections more readily to conspecifics (Bonneaud et al. 2018, Ruden and Adelman 2019, *manuscript in preparation*). Thus, pathology seems to facilitate pathogen transmission (and *V*) in this system.

Tolerance in this system is likely induced by damage-avoidance through a reduction in immunopathology caused by inflammatory responses (Adelman et al. 2013b). While important for killing pathogens, inflammatory responses, including the expression of pro-inflammatory cytokines, can also damage host tissues (i.e., immunopathology) (Graham et al. 2005). Thus, a dampening of these responses can lead to more tolerant phenotypes (Råberg et al. 2009, Sears et al. 2011). Experimental infections suggest that house finch tolerance to MG may occur through down-regulated inflammatory responses. Specifically, individuals with lower expression of a canonical pro-inflammatory cytokine, Interleukin-1β, during MG infection have less severe conjunctivitis and tissue damage, resulting in higher tolerance (Adelman et al. 2013b). Moreover, isolates of finch MG that transmit more efficiently induce higher pathogen burdens, more severe conjunctivitis, and higher expression of a suite of pro-inflammatory cytokines (Williams et al.

2014, Vinkler et al. 2018). Because finches with lower pathology deposit less MG onto fomites, host tolerance through damage-avoidance in this system likely decreases host infectiousness, inhibiting pathogen transmission and decreasing *V* (Fig.2A,B). In support of this, higher tissue-specific tolerance has been associated with a reduced chance of transmission in experimental MG epidemics (Ruden and Adelman 2019, *manuscript in preparation*).

While damage-avoidance mechanisms of tolerance are likely to decrease fitness costs of MG infections and decrease MG transmission, the effects of tolerance through damage avoidance on host-pathogen co-evolution are unknown. As tolerance in this system seems likely to decrease *V* and pathogen transmission, it is possible that as tolerance evolves in house finches, more-virulent MG mutants will gain fitness, as these will be able to increase pathology, enhancing infectiousness and potentially extending the infectious period. In support of this prediction, there has been an increase in virulence among MG isolates since its emergence in house finches, although other factors (such as partial immunity) also contribute to this trend (Fleming-Davies et al. 2018). In general, tolerance through damage-avoidance may be a common host strategy during infections that cause inflammatory damage to mucosal tissues (Råberg et al. 2009, Sears et al. 2011). Thus, these systems are particularly promising for further investigating how tolerance-mediated decreases in pathogen transmission affect host-pathogen co-evolution. Indeed, such studies will be of particular importance to both human and domestic animal health as therapeutics that mimic damage-avoidance tolerance mechanisms become more widely used (Vale et al. 2014).

Damage-Repair: Malaria

Damage-repair mechanisms of tolerance will offset some fitness costs of pathology, but only after this pathology has occurred. This means that when pathology is important for transmission, damage-repair mechanisms will not inhibit transmission and might actually increase overall transmission if tissue repair or replacement prolongs the infectious period (Fig. 1. D,C, Fig. 2. B). Here, we examine how damage-repair mechanisms of tolerance that replace tissues required by malarial pathogens (i.e., red blood cells) may increase the transmission of these parasites among vertebrate hosts.

Malarial pathogens (*Plasmodium sp.*) infect a diversity of vertebrate hosts worldwide, causing an array of disease severity, depending on host and pathogen identity. Malarial sporozoites from the saliva of arthropod vectors (typically *Anopheles* mosquitos) infect vertebrate hosts during blood meals, moving to the liver and reproducing asexually to produce merozoites. These merozoites then leave the liver, infect red blood cells, and undergo another round of asexual reproduction before the blood cells burst, releasing more merozoites. Alternatively, merozoites can develop into immature gametocytes that are taken up by vectors during blood meals (Greenwood et al. 2008).

Given the nature of malaria reproduction within vertebrate hosts, a specific pathology, the rupturing of red blood cells, is inextricably linked to transmission. Without this pathology, merozoite reproduction and the development of gametocytes would cease and hosts would not transmit the pathogen to vectors. In addition, free hemoglobin and pathogen toxins (e.g., hemozoin), released from burst red blood cells can induce other pathologies that are not critical to pathogen transmission, including damaging surrounding cells (Ferreira et al. 2008) and inducing fever (Miller et al. 2013).

Compared to other animal pathogens, tolerance to malarial pathogens is well-studied, particularly in humans and mice (Råberg et al. 2007), and researchers have begun exploring its underlying mechanisms. Of particular relevance to our arguments above, there are several damage-repair mechanisms through which hosts may achieve tolerance during malarial infections. For example, reducing malarial pathogen load reduces pathology (i.e., anemia) (Schoenle et al. 2017), but anemia is also reduced in tolerant individuals without reducing pathogen load (Råberg et al. 2007), suggesting that burst red blood cells may be quickly replaced in tolerant individuals (Medzhitov et al. 2012). Thus, tolerant individuals are guarded against anemia and maintain the overall functionality of the blood as a tissue. Critically, this does not reduce the transmission-relevant pathology of cell bursting. Rather, a quick turn-over of red blood cells and surrounding tissues, without a decrease in pathogen load, likely extends the duration of transmission-relevant pathology (Fig. 1C). Thus, tolerance through efficient damage-repair may extend the infectious period, while having little effect on infectiousness, ultimately increasing overall transmission and V (Fig. 1D). In support of this possibility, asymptomatic carriers of malaria may be an important source of new infections in some systems (Bousema et al. 2004).

Damage-repair mechanisms of tolerance are likely to increase both host and pathogen fitness by decreasing pathology while increasing transmission. Therefore, these tolerance mechanisms could relax selection on virulence and select for malarial pathogens that replicate well, but do not cause increased pathology (but see Metcalf et al., 2012). In addition, because damage-repair mechanisms would enhance transmission, malarial pathogens would not be under intense pressure to subvert this type of tolerance, preserving its fitness-enhancing value for hosts and increasing the chance this trait goes to fixation in host populations. Existing co-evolutionary

models in which tolerance increases pathogen transmission through extending infectious periods or enhancing the probability of contact among hosts (or vectors) should prove useful in understanding how tissue-specific tolerance through damage-repair affects the co-evolution of malarial pathogens and their vertebrate hosts (Boots et al., 2009).

Damage-Avoidance and Damage-Repair: Influenza

Although we have presented damage-avoidance and damage-repair mechanisms of tolerance as distinct, these are not mutually exclusive. Damage-avoidance mechanisms may decrease transmission-relevant pathology and host infectiousness at the same time that damage-repair mechanisms rapidly generate healthy tissues that pathogens can exploit, extending the host's infectious period (Fig. 1 E,F, Fig. 2 A,B). Here, we discuss the potential effects of both damage-avoidance and damage-repair mechanisms of tolerance on the transmission of influenza viruses.

Influenza viruses (Family *Orthomyxoviridae*) cause acute upper respiratory tract infections in many vertebrates, particularly mammals and birds. After infection, influenza begins reproducing in respiratory epithelial cells and hosts typically begin shedding virions in nasal secretions within 24 hours. Influenza can be transmitted through both direct and indirect (through fomites) contact, as well as through aerosolized respiratory droplets (Bean et al. 1982, Tellier 2006, Mubareka et al. 2009, Pica and Bouvier 2012, Thangavel and Bouvier 2014), although the importance of airborne transmission in some host species is unclear (Brankston et al. 2007). The efficiency of transmission likely depends on the amount of virus shed into the environment (Bean et al. 1982, Mubareka et al. 2009), although few experimental studies of influenza have simultaneously measured the amount of shed pathogen and transmission rates. Nasal viral titers are more frequently measured and can correlate with both shedding into the environment and

transmission rates, though there is substantial variation in these patterns (Mubareka et al. 2009, Milton et al. 2013).

Variation in the relationship between nasal viral titers and transmission suggest that additional factors, such as the severity of pathology, may drive viral shedding and transmission. There is some evidence for this pattern in humans, as symptomatic individuals are more likely to shed viral particles than are asymptomatic individuals (Huang et al. 2011). Moreover, the severity of self-reported symptoms are positively associated with viral shedding (Yan et al. 2018). Pathology resulting from influenza infection typically includes a cough, pharyngitis, and nasal discharge, as well systemic symptoms such as fever, myalgia, and malaise (Treanor 2010), with several of these pathologies likely to increase viral transmission. For example, coughing during infection typically expels influenza virus, most often in aerosolized particles of the correct size to be inhaled by other hosts (Lindsley et al. 2012). Coughing frequency is also positively correlated with viral shedding in humans (Yan et al. 2018). Thus, pathology that increases coughing frequency (such as extensive immunopathology) may result in increased influenza transmission. Pathology that increases mucosal secretions may also be important in the transmission of influenza. Mucosal secretions from the conjunctiva and nasal passages carry influenza and can contaminate fomites or lead to direct transmission to other hosts (Weber and Stilianakis 2008). Furthermore, the addition of mucus to a viral inoculum increases the amount of time influenza virus can survive on fomites (e.g., paper money; Thomas et al. 2008). Together, these results suggest that pathology likely facilitates transmission during influenza infections.

Hosts can achieve tolerance during these infections through a variety of mechanisms (reviewed in Iwasaki and Pillai 2014), including both damage-avoidance and damage-repair.

Mechanisms of damage-avoidance are likely to be important as severe cases of influenza can result from overresponsive inflammatory responses in humans (Tisoncik et al. 2012), mice (Srivastava et al. 2009), and ferrets (Kang et al. 2011, Maines et al. 2012). Indeed, during influenza infection, there is a positive correlation between pulmonary pathology and gene expression of pro-inflammatory immune factors (Kash et al. 2004, 2006). Levels of pro-inflammatory cytokines (including TNF-alpha and IL-6), are also positively correlated with pathology, as well as pathogen load in the nasal passages and airborne transmission efficiency (Maines et al. 2012). Thus, tolerance mechanisms that reduce the inflammatory response will allow hosts to avoid excessive damage from immunopathology (Williams et al. 2005, Snelgrove et al. 2008). Moreover, tolerance to influenza through damage-avoidance can also be induced with therapeutics: inflammatory responses can be dampened (through the administration of tumor necrosis factor (TNF) antagonists; Hussell et al. 2001) and respiratory epithelial cells can be protected from immune-generated reactive oxygen species using antioxidants (Shi et al. 2013). Because such mechanisms should decrease pathologies that enhance transmission, we would predict tolerance via damage-avoidance to decrease transmission during influenza infections (Fig. 1A,B).

However, hosts could also achieve tolerance to influenza via several damage-repair mechanisms. For example, certain pattern recognition receptors expressed by immune and epithelial cells in the bronchus (e.g., the NOD-, LRR- and pyrin domain-containing 3 inflammasome) are activated in response to host cell damage and stimulate tissue repair (Thomas et al. 2009). Regulatory T-cells (T_{regs}) also play a role in tissue repair after infection by secreting amphiregulin, the absence of which results in more severe lung damage during influenza infection (Arpaia et al. 2015). These repair mechanisms help replenish cells necessary for

influenza replication, potentially increasing infection duration. Thus, tolerance likely has complex impacts on influenza transmission, enhancing it in some ways and inhibiting it in others (Fig. 1E,F).

As the interactions between damage-avoidance and damage-repair mechanisms have opposite effects on pathogen transmission, they are also likely to have opposite effects on the evolution of pathogen virulence, as discussed in previous sections. Whether influenza viruses are ultimately selected for higher or lower virulence may depend on the relative strength of these two types of mechanisms. Such dual effects may prove common across viral and other infections, reinforcing the importance of fully understanding tolerance mechanisms in revealing the factors that drive variation in transmission and host-pathogen co-evolution.

Concluding Remarks

Here, we contend that tolerance does not necessarily increase pathogen transmission. Rather, the effect of tolerance on pathogen transmission and host competence should vary with the specific mechanisms involved. In particular, tissue-specific tolerance driven by damage-avoidance will decrease overall transmission, whereas tissue-specific tolerance driven by damage-repair will increase overall transmission. Further, these different mechanisms of tissue-specific tolerance may have opposite implications for the evolution of pathogen virulence and host-pathogen co-evolution.

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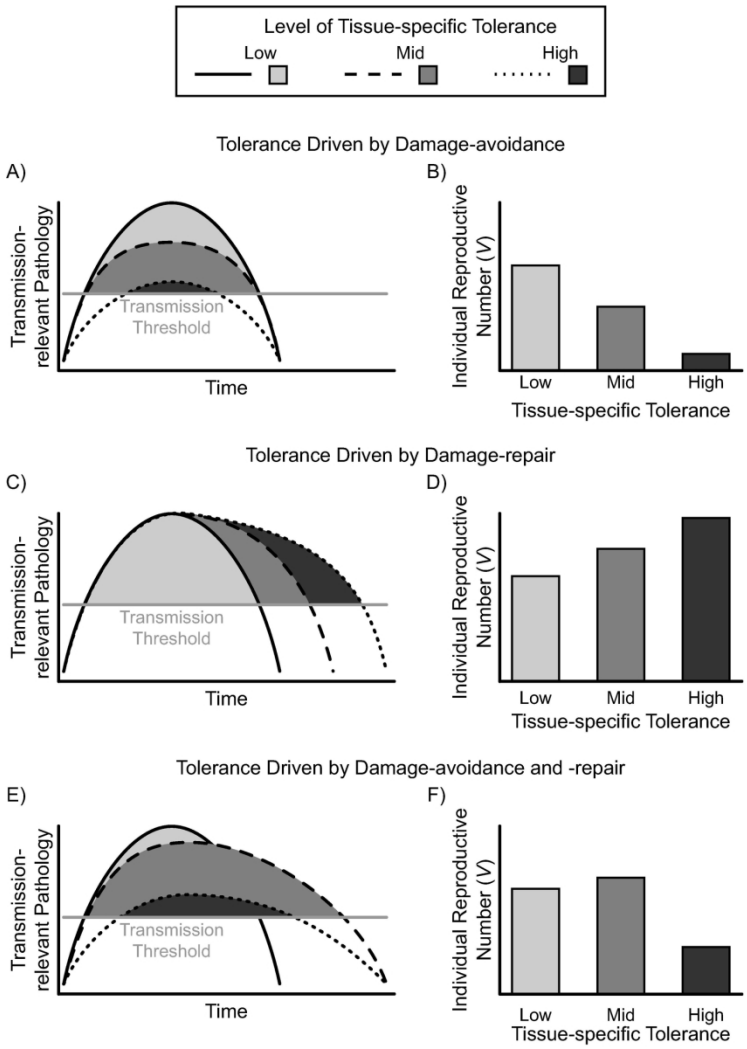
Figure Legends

Figure 1. Depending on its underlying mechanisms, tissue-specific tolerance can either enhance or diminish a host's ability to cause new infections (individual reproductive number, *V*). Shading represents relative amounts of transmission relevant pathology (A,C,E) and individual reproductive number (B,D,F) under low (light shading), medium (intermediate shading), and high (dark shading) levels of tissue-specific tolerance. When hosts rely on damage-avoidance mechanisms (A,B), tolerance reduces transmission-relevant pathology, so decreased infectiousness and can shorten the infectious period, reducing *V*. In contrast, when hosts rely on damage-repair mechanisms, tolerance does not reduce pathology relevant to transmission, e.g., red-blood cell lysis during malaria, so does not alter infectiousness, but does prolong the infectious period, increasing *V* (C,D). Finally, when hosts employ both mechanisms, relative changes in *V* will depend on which mechanism is dominant (E,F). When damage-avoidance is the dominant mechanism of tolerance, the infectious period may be extended but infectiousness will decrease, ultimately decreasing *V* (illustrated by the high tolerance example in panels E and F, dark shading). When damage repair is the dominant mechanism, the infectious period is again extended but infectiousness is only moderately lowered, ultimately increasing *V* (illustrated by the medium tolerance example in panels E and F, intermediate shading).

Figure 2. The effects of tolerance on individual reproductive number (V) depends on the mechanisms through which tolerance is achieved. Tolerance through damage-avoidance (A) limits the severity of transmission-relevant pathology, reducing infectiousness, potentially decreasing the duration of the infectious period, and thus decreasing V. Tolerance through damage-repair (B) does not affect the severity of transmission-relevant pathology, but increases the duration of pathology and thus the infectious period, ultimately increasing V.



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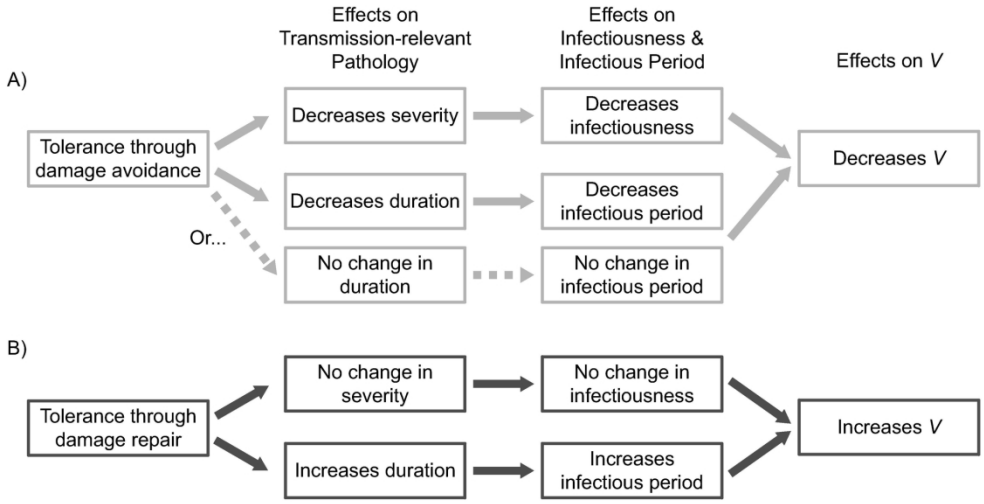

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