Evolution of pathogen tolerance and emerging infections: A missing experimental paradigm

Srijan Seal1*, Guha Dharmarajan2, Imroze Khan1*

1Ashoka University, Sonepat, India; 2Savannah River Ecology Laboratory, University of Georgia, Aiken, United States

Abstract Researchers worldwide are repeatedly warning us against future zoonotic diseases resulting from humankind’s insurgence into natural ecosystems. The same zoonotic pathogens that cause severe infections in a human host frequently fail to produce any disease outcome in their natural hosts. What precise features of the immune system enable natural reservoirs to carry these pathogens so efficiently? To understand these effects, we highlight the importance of tracing the evolutionary basis of pathogen tolerance in reservoir hosts, while drawing implications from their diverse physiological and life-history traits, and ecological contexts of host-pathogen interactions. Long-term co-evolution might allow reservoir hosts to modulate immunity and evolve tolerance to zoonotic pathogens, increasing their circulation and infectious period. Such processes can also create a genetically diverse pathogen pool by allowing more mutations and genetic exchanges between circulating strains, thereby harboring rare alive-on-arrival variants with extended infectivity to new hosts (i.e., spillover). Finally, we end by underscoring the indispensability of a large multidisciplinary empirical framework to explore the proposed link between evolved tolerance, pathogen prevalence, and spillover in the wild.

Introduction

The frequent emergence of infectious diseases from wildlife and cross-species spillover has transformed the curiosity of understanding the natural variation in host-pathogen interactions into a pressing need (Bloom et al., 2017; Cunningham et al., 2017). Detailed knowledge of circulating pathogenic strains and heterogeneities in infection outcomes and disease dynamics can shed light on potential future transmission events. Tracking ecological conditions underlying spillover events, where zoonotic pathogens overcome the species barrier (i.e., a hindrance to interspecies transmission) to infect a novel host, can be beneficial for predicting the emergence and spread of pathogens. So, what facilitates such spillover? While we have just begun to understand the patterns and processes underlying emerging infectious diseases (EIDs), earlier surveillance of wild animals that are typically known to harbor zoonotic pathogens has revealed certain intriguing trends (Morse et al., 2012). Hosts that are phylogenetically related tend to share a common pathogen pool, and thus have increased potency to cross-infect each other (Shaw et al., 2020; Wolfe et al., 2007). For example, it is already known that primates harbor a diverse array of pathogens capable of causing severe diseases in humans (Han et al., 2016), including parasites such as Plasmodium knowlesi (Sabbatani et al., 2010) or simian immunodeficiency virus (SIV) that underwent host-switching and is the most common ancestor of the human immunodeficiency virus (HIV) (Sharp and Hahn, 2011). Perhaps, in such cases, pathogens do not require major adaptations to spill over into phylogenetically closer organisms due to a relatively lower species barrier (e.g., comparable immune responses and physiological processes), thereby increasing the spillover efficiency. Spatial proximity with reservoir hosts can also lead to increased spillover risk (Davies and Pedersen, 2008). This is exemplified by a diverse array of synanthropic (e.g.,
brown rat, *Rattus norvegicus* and domestic (e.g., dog, *Canis lupus familiaris*) species that are known to share more zoonotic pathogens with humans than other animal taxa (Gibb et al., 2020; McFarlane et al., 2012), thereby increasing the risk of host shift. However, in these examples, in addition to spillover via phylogenetic relatedness or spatial proximity, arguably, another important condition can be the circulation of a stable, large, and diverse zoonotic pool in the reservoir species. Indeed, this is corroborated by recent analyses and mathematical models indicating that the number of zoonotic viruses with spillover risk might increase proportionally with the total number (Mollentze and Streicker, 2020) as well as the genetic diversity (Remien and Nuismer, 2020) of viruses maintained inside reservoir animals.

How do reservoir species manage to support the circulation of zoonotic pathogens? The answer perhaps lies in specific ecological, life-history, and physiological features of reservoir hosts that allow both a stable circulation of zoonotic pathogens as well as their continuous shedding into the environmental niche shared with other susceptible species (Gibb et al., 2020). For instance, naive Egyptian fruit bats (*Rousettus aegyptiacus*) can remain infected with the Marburg virus for 7 months after inoculation (Schuh et al., 2017) with little or no clinical disease symptoms. Meanwhile, they can also spread the infection efficiently by contiguous shedding into the ecological space that they share with their conspecifics as well other species, including primates (Rasche et al., 2016). In other less-known reservoirs such as water buffalo (*Bubalus bubalis*), a small number of individuals can shed *Brucella abortus*, the causative agent of brucellosis, persistently at a high level for more than 2 months (Capparelli et al., 2009). Persistent shedding of circulating strains of pathogenic *Escherichia coli* such as O157:H7 from various cattle species has already been reported to cause global outbreaks of gastrointestinal illness in humans (Stein and Katz, 2017). The pertinent question here is, of course, what prevents reservoir animals from eliminating these pathogens via effective immune responses? Although the mechanisms are unclear (Gal-Mor, 2018), these examples perhaps hint at the unique adaption of their immune system. Understanding the ecological contexts and evolution of such interactions between the host immunity vs. pathogens is thus necessary not only to explain the persistence of zoonotic pathogens but also to predict how and when the next spillover may happen.

There is also a growing interest to elucidate the factors driving heterogeneous infection outcomes in reservoir vs. new hosts (VanderWaal and Ezenwa, 2016). For instance, original animal reservoirs harboring pathogens capable of causing severe diseases in other animal hosts, including humans, often do not show disease symptoms themselves (Baker et al., 2013; Guito et al., 2021; Pandrea and Apetrei, 2010). Bats and rodents, which harbor more than 60 % of known zoonotic pathogens, are classical examples of such reservoir hosts (Jones et al., 2008) as they are capable of asymptotically carrying a high diversity of human pathogens, including coronaviruses, henipaviruses, filoviruses, and hantaviruses (reviewed in Subudhi et al., 2019). Recent studies indicate that they are efficient reservoir hosts because their dampened innate immune pathways do not form effective barriers to prevent viral infections, thereby allowing viruses to easily establish stable infection inside the host (Letko et al., 2020). Such reduction in immune responses could also protect hosts from negative consequences of immune activation (Khan et al., 2017a) because, contrary to our expectation, disease symptoms are not always caused by ineffective immune responses, but are often mediated via their overreactivity (Graham et al., 2005). For instance, patients infected with HIV or influenza viruses have high levels of type 1 interferon (IFN) and T-cell activation (Teijaro et al., 2011), which also impose cytotoxicity and immunopathological damages (self-harm) to their own cells and organs (Dybdahl and Storfer, 2003; Hsue et al., 2004; Kaplan et al., 2011). This is possibly also true in the case of the ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, Dec 2019 to present), which has already caused more than 4.1 million deaths within 1.5 years (https://covid19.who.int/). Growing evidence suggests that besides causing severe flu-like symptoms in humans (Harrison et al., 2020), SARS-CoV-2-driven increased morbidity is also associated with a ‘cytokine storm’ comprising surplus release of tumor necrosis factor-α (TNF-α) and IFN-γ (Ayres, 2020; Azkur et al., 2020), triggering multiorgan failure and sepsis (Hu et al., 2021). Certainly, the answers to such heterogeneous infection outcomes perhaps lie in – why do different hosts, in the first place, employ distinct immune response strategies against the same pathogen?

Unfortunately, our understanding of infection and disease has been overtly biased by how we perceive pathogens that infect us. Since pathogens by definition reduce host fitness (e.g., through increased mortality or reduced fecundity), host-pathogen interactions have been traditionally viewed
as purely antagonistic. Consequently, studies on pathogen defense have primarily focused on mechanisms that host typically use to resist infections by activating immune responses (Ayres and Schneider, 2012). This bias has led us to ignore mechanisms that facilitate the host’s ability to coexist with pathogens and withstand their negative fitness effects by reducing pathogen- or immune-mediated damage (i.e., tolerance; see Figure 1; McCarville and Ayres, 2018; Råberg et al., 2009; Råberg et al., 2007; Schneider and Ayres, 2008). Such a response to tolerate pathogens and their effects is perhaps a more meaningful strategy from the reservoir host’s perspective (discussed later). Contrary to pathogen resistance, since tolerance mechanisms mitigate fitness costs without directly changing the pathogen burden, they can explain their high abundance and longer persistence required for effective transmission of emerging infections (Mandl et al., 2015; Oliveira et al., 2020). However, despite the proposed link (e.g., high circulation of Marburg virus in bat hosts; Guitò et al., 2021) or SIV in simian hosts, (Chakrabarti, 2004) causal connections between tolerance, pathogen circulation, and risks of emerging infections in the natural host-pathogen systems have been rarely analyzed (but see Guitò et al., 2021); for example, at an ecological scale, how do host immune strategies and pathogen populations interact to modulate the risk of emerging infections? Indeed, studies of several emerging viral diseases in human cell lines and other laboratory models have been highly successful in shedding light on proximate host defense mechanisms and counter-strategies used by viruses (LeGrand et al., 2006). Yet they might not be the best system to understand infections in their natural hosts (Bean et al., 2013) and simulate situations where they can become an emerging infection in the wild (Flies, 2020a).

In this review, we are primarily addressing how disease tolerance in reservoir species can be intrinsically linked to the maintenance and transmission of pathogens and their spillover. We first discuss why and how tolerance might naturally evolve during long-term association between natural hosts and pathogens as an effective strategy. We then outline the favorable ecological and evolutionary contexts vis-à-vis host-pathogen tolerogenic interactions that may maximize the spillover risk (see Figure 2 for a brief conceptual outline). Besides host immune modulation, we note that tolerance may also evolve because pathogens can adapt to cause less harm to their hosts. Finally, we end by highlighting the importance of a systematic empirical framework to test various hypotheses on disease

Figure 1. Outlining the difference between resistance vs. tolerance. Defense mechanisms against invading pathogens can either include eliciting immune responses to detect and eliminate pathogens (resistance) or mitigate the fitness costs of infection or immune activation without directly reducing the pathogen load (tolerance). Different genotypes are initially exposed to the same number of pathogens. Figure plotted based on hypothetical data and adapted from Figure 1 of Råberg et al., 2007.
tolerance and its plausible evolutionary ecological role in emerging infections. With growing evidence of disease tolerance in natural host-pathogen systems, we hope that its detailed understanding might provide new impetus to infectious disease research and pandemic preparedness.

Relevance of evolving tolerance in natural host-pathogen systems

Immune strategies are not only contingent on how hosts and pathogens interact but also depend on their specific ecological and life-history contexts. Depending on the pathogenicity and infection frequency, the host’s optimal immune response might rapidly change (Khan et al., 2017b; Sorci, 2013). While killing invading pathogens by activating immunity seems to be the most obvious choice for hosts to respond against infection, such resistance mechanisms can themselves lead to negative fitness consequences via immunopathological damages (Khan et al., 2017a; Schneider and Ayres,
2008). Depending on what types of cells and organs are getting damaged, immunopathology can ultimately lead to disruption of normal physiology and impose lifelong pathological consequences (Auten and Davis, 2009; Khan et al., 2017a). Do high costs of such inflammatory responses against pathogens tilt the balance in favor of a tolerance strategy over an evolutionary time scale? Although there are no experiments to detect such dynamic changes in immune strategies, one possibility is that if the activation of the immune response causes proportional damage to both the host and the pathogen, then the host’s ability to invest in self-toxic immune responses might have an upper limit. Beyond this threshold, the host may switch strategy from active resistance to tolerating infections to limit the immunopathological damages. However, tolerance to invading pathogens might also have a threshold, especially when invading pathogens exploit the host resources, and hence, an unlimited number of pathogens is not sustainable. Therefore, optimal use of immune strategies is perhaps fine-tuned by the fitness effects of both immune activities and pathogen statistics (Mayer et al., 2016).

**Tolerance in natural hosts and disease reservoirs**

Recent experiments in naturally occurring systems have provided ample evidence for disease tolerance in nature, although exact ecological contexts are widely varied and detailed micro-evolutionary processes remain unclear. For example, the West Nile virus causes significant population declines in most avian hosts, but not in mourning doves (Zenaida macroura) where individuals can harbor high viral titers without showing any significant morbidity, suggesting features of infection tolerance (Komar et al., 2003; LaDeau et al., 2007). Hawai’i ‘Amakihi (Hemignathus virens) from low-elevation regions show a reduced rate of weight loss and better physiological condition even during the acute-phase infection with Plasmodium relictum than their high-elevation counterparts, indicating their higher tolerance to pathological effects of avian malaria (Atkinson et al., 2013). In the wild-caught field voles (Microtus agrestis), mature males can maintain better body condition than immature males while harboring very high macro- and micro-parasite loads, again indicating a higher tolerance (Jackson et al., 2014). Older tadpoles of American toad (Bufo americanus) and green frogs (Rana clamitans) also show characteristics of relatively higher tolerance to Echinostoma trivolvis, a locally abundant trematode species, compared to younger tadpoles (Rohr et al., 2010). Besides showcasing tolerance in natural populations, these examples also highlight how tolerance response in the wild is sensitive to species identity, population history, and their life-history traits.

Molecular information underlying the host’s responses against their natural pathogens further revealed that several key reservoir species have consistently evolved mechanisms to mitigate the immunopathological consequences caused by the over-induction of inflammatory pathways (Letko et al., 2020). A very recent analysis showed that fruit bats (R. aegyptiacus), the natural reservoirs for the Marburg virus, lack the induction of several pro-inflammatory genes that are classically implicated in primate filoviral pathogenesis such as CCL8, FAS, and IL6 (Pavlovich et al., 2018). While they have expanded the type I IFN gene family, which is known to initiate an antiviral immune cascade with reduced inflammatory capacity, they also seem to use natural killer (NK) cell receptors with distinct inhibitory signaling components, allowing them to asymptptomatically harbor high viral loads (Pavlovich et al., 2018). Also, the PHYIN family of genes and sets of innate immune receptors/sensors capable of activating inflammasome were shown to be absent in two bat species, Pteropus alecto and Myotis davidii (Ahn et al., 2016). Using different types of RNA viruses such as influenza A virus, Melaka virus, and Middle East respiratory coronavirus, researchers have shown that dampening inflammatory responses enable these bats to tolerate multifarious viral infections (Ahn et al., 2019), avoiding immunopathological damages caused by cytotoxic intermediates (Letko et al., 2020; Subudhi et al., 2019). The reduction in cytotoxic inflammatory responses in bats has been further proposed to have coevolved as a response to minimize DNA damage, caused by free radicals generated during their increased metabolic activity while flying (Irving et al., 2021; Zhang et al., 2013). Such mechanisms also highlight the liaison between bat immunity and key life-history adaptations.

Interestingly, sooty mangabeys (Cercocebus atys) and African green monkeys (Chlorocebus aethiops) infected with SIV show acute early inflammation, but they also possess regulatory mechanisms to rapidly control such responses; for example, they use anti-inflammatory inhibitory cytokines such as transforming growth factor-β (TGF-β) and IL-10 (Silvestri et al., 2007) to avoid chronic aberrant immune activation and immunopathology (Ansari and Silvestri, 2014; Pandrea et al., 2008; Silvestri et al., 2003). Besides, they are also able to maintain normal rates of peripheral mature CD4+ T-cells sensitive to species identity, population history, and their life-history traits.
T cell proliferation to compensate for the cytopathic destruction of CD4+ T cells post-viral infection (Chahroudi et al., 2012). The role of immunomodulatory molecules is widespread in other reservoir species as well. In rodents, regulatory T cell (Treg) responses suppress inflammation and downregulate cytotoxic T lymphocyte responses that usually eradicate the virus-infected cells, thereby facilitating viral persistence inside hosts (Robertson and Hasenkrug, 2006). For example, hantavirus-infected rodents maintain a steady-state Treg response to allow viral persistence as well as to curb inflammation-induced immunopathology (Schountz and Prescott, 2014). Deer mice (Peromyscus maniculatus) infected with Sin Nombre virus (SNV) also upregulate cytokines that correspond to Treg responses, prolonging the viral presence (Ermonval et al., 2016). Norway rats (R. norvegicus) infected with Seoul virus (SEOV) not only reduce the pro-inflammatory mediators such as interleukin-6 (IL-6) or TNF-α in their lungs but also increase the expression of regulatory factors TGF-β (overexpressed in bats as well; Silvestri et al., 2007) and FoxP3 to prevent inflammation-related pathology at sites of increased SEOV replication (Easterbrook and Klein, 2008). A growing body of evidence for pathogen tolerance is also coming from arthropod vectors, evolving various mechanisms to efficiently repair the damages caused by pathogens. This in turn allows them to have a normal lifespan while carrying persistent infections. For example, while dengue virus infection in Aedes aegypti causes apoptosis in the midgut, mosquito hosts improve the maintenance of midgut homeostasis and tissue integrity via careful regulation of interstitial stem cell (ISC) proliferation, tolerating the effects of viral infection (Oliveira et al., 2020). Another example includes arboviral infection, which usually leads to oxidative stress in insect cells (Joubert et al., 2012), but mosquito vectors can tolerate the infection by upregulating their antioxidant pathways in the midgut (Tchankouo-Nguetcheu et al., 2010; Cappuccio and Maisse, 2020).

Taken together, it appears that reservoir hosts and vectors might have repeatedly evolved either lower inflammatory responses or multifarious compensatory mechanisms to mitigate the negative effects of inflammation. The ability to maintain a balanced immunity and homeostasis during infection might explain their ability to tolerate the circulating pathogens, without showing severe disease symptoms. Yet, a major gap in our understanding is that none of these previous experiments could reveal how these features arose in these animals.

So, what drives the evolution of tolerance?

Although experimental results are limiting, one of the most compelling results in recent years was obtained from longitudinal sampling of wild Soay sheep (Ovis aries) populations performed by Hayward and coworkers (Hayward et al., 2014). They not only showed tolerance in wild sheep populations against their naturally occurring intestinal worms but also provided the conceptual framework for how natural selection might have acted upon tolerance (Hayward et al., 2014). For instance, individuals losing bodyweight more slowly with increasing pathogen burden (i.e., more tolerant, Figure 1) had higher lifetime reproductive success, suggesting a strong positive selection on tolerance. However, the most striking feature of their results was that the observed variations in tolerance were mostly explained by the environmental effects, with very little additive genetic variation left in the population, thereby indicating that tolerance evolved under a strong directional selection. These results conform with existing theoretical models that predicted tolerance to reduce polymorphism, underscoring the importance of directional selection therein (Miller et al., 2005). In other words, as the infection spreads, consistently higher fitness advantage of tolerant hosts than their nontolerant counterparts might reduce the levels of genetic variation and cause rapid fixation of tolerance-related alleles (Miller et al., 2005; Roy and Kirchner, 2000). This is in stark contrast to resistance strategy, which typically reduces pathogen fitness, instigating an evolutionary arms race to select for pathogen traits to overcome the host’s resistance mechanisms (Schneider and Ayres, 2008). However, high costs of immune activation and life-history trade-offs might cause resistance alleles to converge to an intermediate optimum under stabilizing selection (Råberg, 2014). Individuals can also maintain genetic variation for resistance under balancing selection (Råberg, 2014), which might produce highly polymorphic infection outcomes within the population (Lefèvre et al., 2010).

Notably, understanding the evolutionary origin of pathogen tolerance in the wild might require information on the long-term coevolutionary history of natural reservoirs and their pathogens. In most cases, it is quite difficult to validate a causal link between coevolutionary history and micro-evolutionary processes leading to the evolution of tolerance in natural hosts, but a few recent comparative analyses...
offer some interesting clues. A key experiment with populations of house finches (Haemorhous mexicanus) from two locations with a different coevolutionary history of infection by bacterium Mycoplasma gallisepticum was particularly helpful here (Adelman et al., 2013). The population from Alabama with a longer history of exposure to M. gallisepticum infection showed higher tolerance than the population from Arizona, which was not exposed to the pathogen previously. This is further supported by mechanistic studies, which revealed that the more tolerant Alabama population expressed lower levels of pro-inflammatory cytokine (IL-1β) and higher levels of anti-inflammatory cytokine (IL-10) (Adelman et al., 2013). In another example, natural populations of Asian tiger mosquitoes (Aedes albopictus) isolated from regions with longer exposure to heartworm (Dirofilaria immitis) also showed higher tolerance compared to populations with little exposure to the parasite (Dharmarajan et al., 2019). These results might have negative implications for human health as tolerant mosquitoes with increased vectorial capacity might catalyze the disease spread (Dharmarajan et al., 2019; Lefèvre et al., 2013). In rodents, phylogenetic analyses have revealed that hantaviruses became associated with ancestral rodents of the family Muridae (Plyusnin and Morzunov, 2001). Subsequently, when the ancestral family underwent co-speciation events resulting in different subfamilies such as Murinae, Arvicolinae, and Sigmodontinae, hantaviruses remained associated with them, thereby explaining their continued persistence and asymptomatic state of several rodent species (Plyusnin and Morzunov, 2001; Schountz and Prescott, 2014). Finally, sooty mangabeys and African green monkeys, natural hosts of SIV, also remain healthy and do not develop AIDS (Chahroudi et al., 2012; Wetzel et al., 2017) possibly because of their long coevolutionary history with lentiviruses (dating back to 5–6 million years; Compton and Emerman, 2013), which enables them to prevent the deleterious consequences of SIV infections (Rudensey et al., 1995). Taken together, while these examples unanimously suggest the importance of long-term host-pathogen coevolutionary dynamics in pathogen tolerance, they also indicate that such a response is perhaps unlikely to be true for host species exposed to novel pathogens that they have not coevolved with.

**Implications of land-use changes**

In recent decades, the altered trajectory of host-pathogen interactions and coevolutionary dynamics might have more obvious consequences for disease spread from animals to humans, associated with rapid deforestation and land-use changes (Bloomfield et al., 2020; Plowright et al., 2021). For example, landscapes with patches of forests are likely to have increased spatial overlap between wildlife, livestock, and humans. This presents ideal ecological conditions for transmission of zoonotic pathogens from naturally tolerant wildlife hosts, thereby increasing the risk of disease outbreaks in nearby domestic animal or human populations (Hansen et al., 2013; Rulli et al., 2017). In 2019, 14 Chinese workers died in Guyana (South America) while engaged in mining due to infection caused by the fungus Histoplasma, rarely found in China but prevalent in America, mostly isolated from soil samples containing decaying bat and bird feces (Wang et al., 2019). This might be an example of how the invasion of humans into the natural ecosystem can expose them to local new infections for which they lack effective immune responses. While it will remain unclear whether the outcome would have been different if Chinese populations had shared evolutionary history with Histoplasma in their natural habitat, revealing the causality between coevolution, tolerance, and infection will be a formidable challenge for understanding new EIDs in the wild, warranting closer investigation.

**Role of tolerance in spillover and new infections**

Successful spillover to novel host warrants multiple sequential steps (Plowright et al., 2017). Briefly, pathogens should first be released by their reservoir hosts either directly into the environment or a new host through different plausible transmission routes such as consumption, animal bites, or sexual interactions (Webster et al., 2017). Pathogens should then survive until it encounters novel susceptible hosts whom it might infect directly or by undertaking a further round of adaptation to the new host environment (Parrish et al., 2008). Finally, once the pathogen establishes infection in the novel host by evading the immune responses, it then needs to spread effectively in the population (Plowright et al., 2015; Subudhi et al., 2019). At each step of this transmission chain, the duration of the host’s infectivity, population density, and size might dictate the success of the consecutive step (Remien and Nuismer, 2020; Wolfe et al., 2007). However, before all these fine-scale micro-evolutionary
downstream processes can begin, potentially an important precondition can be the maintenance of a sufficiently large (Mollentze and Streicker, 2020) and diverse (Remien and Nuismer, 2020) zoonotic pathogen pool with the potential to overcome the species barrier. Although the causal link is absent, large populations of reservoir animals harboring large pathogen populations have been predicted to serve as fertile sources of zoonotic diseases (Han et al., 2016). Also, the role of reduced inflammation and disease tolerance in maintaining such persistent zoonotic pathogen populations in reservoir species has already been implicated (Pavlovich et al., 2018; Martin et al., 2019), but how it can boost transmission and spillover is relatively unclear.

**Tolerance might enhance spillover risk by increasing the infectious period, pathogen burden, and genetic diversity**

Physiological mechanisms underlying the tolerance response might be critical in triggering the spillover process (Medzhitov et al., 2012; Henschen and Adelman, 2019). For example, both infectious period and transmission potential can increase if the host tolerates the pathogenic infection by evolving an efficient repair mechanism to counter the damages caused by the pathogen and immune responses (Henschen and Adelman, 2019). The host can generate new cells to replace injured tissues (Medzhitov et al., 2012), as observed in the case of micro-hemorrhages caused by metazoan parasites like Schistosoma mansoni or ruptured red blood cells by Plasmodium sp. (Allen and Wynn, 2011; Henschen and Adelman, 2019). Such a mechanism can allow pathogens to continuously infect new cells, thereby reducing the selection pressure on them to replicate more effectively (Henschen and Adelman, 2019). Consequently, this whole process might select less virulent pathogens for reservoir hosts (Miller et al., 2006), resulting in a longer infectious period and higher number of circulating pathogens, extended pathogen shedding duration, and increased risk of contacts among infected and susceptible hosts (Adelman and Hawley, 2017; VanderWaal and Ezenwa, 2016). These hypotheses are also consistent with a previous theoretical model, which suggests that tolerance can increase the overall disease burden in host populations, by transmitting the infection to other nontolerant susceptible individuals sharing the same ecological niche (Horns and Hood, 2012). The model further predicts that because of such increased disease burden tolerance is most effective in small and isolated host populations, where the risk of infection transmission to other susceptible individuals can be minimized, suggesting a joint role of demographic features and tolerance on disease spread. A recent study on African straw-colored fruit bats (Eidolon helvum) strongly supports this possibility where small isolated populations had a higher abundance of henipaviruses and extended within-host latency (Peel et al., 2018). Although not tested empirically, spatial proximity to these populations can certainly increase the risk of infections to conspecific susceptible individuals as well as spillover to new hosts.

It is also important to note that spillover into a new host is a rare event (Cross et al., 2019) where pathogen abundance alone may not be always sufficient to jump across the species barrier. Although not mutually exclusive, the emergence of novel zoonotic pathogens might also depend on the genetic diversity of the pathogen pool (Wolfe et al., 2007). Pathogen genetic diversity is likely to be greatest within large reservoir populations when they also harbor proportionally large pathogen populations (Remien and Nuismer, 2020). Increased strain diversity might enhance the pathogen’s prospect of jumping across species barrier by harboring the pool of useful mutations to establish infection in a new host (Dennehy et al., 2010; i.e., production of specific rare variants that are inherently more competent to establish cross-species infection; Mandl et al., 2015). Indeed, changes in genetic diversity of the pathogen pool by mutations or genetic exchanges can lead to alterations in the kinetics of viral replication within the natural hosts (Simmonds et al., 2019), modulating the host’s ability to detect antigens and initiate countereffective immune responses (Burmeister et al., 2016; Retel et al., 2019).

**Tolerance vs. pathogen interactions**

An interesting situation might arise when hosts harbor multiple pathogen strains thriving together, increasing the level of competitive interactions (Miller et al., 2006). It has been shown that under intense intra-specific competition for available hosts, bacteriophage φ6 that normally infects Pseudomonas syringae can also rapidly evolve to infect other novel bacterial hosts such as Pseudomonas atrofaciens and Pseudomonas glycinea (Bona et al., 2013). While this provides a clear example where the ability to infect new hosts arose as a function of intra-specific competitive interactions, it might
be relevant for increased disease transmission and spillover as well, provided the probability of such interactions between zoonotic pathogen strains intensifies inside reservoir hosts. Extended infectious period, higher abundance, and relaxed selection within naturally tolerant hosts can certainly provide the appropriate stage for pathogens to acquire mutations to evolve into a new strain or exchange genetic material between various strains (Domingo-Calap, 2019). These are perhaps more likely for pathogens with multi-segmented genomes such as the influenza virus, where rapid viral replication can increase diversity by allowing the recombination of different genonomic segments (McDonald et al., 2016). Revealing the plausible ecological contexts that increase the chances of reassortment (e.g., presence of co-infecting strains; Tao et al., 2015) might be crucial to tracing how novel genome combinations can arise to create influenza subtypes with expanded host range and novel antigenic properties (Bhat et al., 2021; also see Cecilia, 2014 for recombined dengue virus genotypes).

Another plausible example is the gene loss and adaptations during interspecies transmission of SIVcpz, a strain of SIV that naturally infects chimpanzees. Later analyses revealed SIVcpz as a recombinant between two SIV lineages from old-world monkeys with a uniquely reconstructed vif gene (Bailles et al., 2003; Etienne et al., 2013). Although it is unclear where and how such genetic modification took place, this enabled the recombinant virus to antagonize hominid antiviral protein APOBEC3s more efficiently, contributing to the origin of the HIV-1 pandemic in humans (Etienne et al., 2013). Most recently, the phylogenetic network approach has revealed that even the VOC202012/01 variant of SARS-CoV-2, which was first reported in the UK in 2020, might have originated through recombination of preexisting virus strains before rapidly spreading into many other countries (Xie et al., 2021). Although direct evidence is lacking, the role of suitable human hosts tolerating the coexistence of multiple strains cannot be ignored (Martin et al., 2011; Simon-Loriere and Holmes, 2011). This is partly corroborated by recent evidence of SARS-CoV-2 evolution in immunocompromised patients who could maintain high viral loads over prolonged periods (reviewed in Day et al., 2020), thereby allowing more opportunities for viral replication, mutations, and potential recombination events.

In contrast, recombination between unrelated groups of viruses is rare, but such situations can also arise, at least ecologically, if they coexist within a tolerant host, serving as a unique niche for them to stay together for long, interchange genomic sequences and undergo recombination to create viral strains with emergent properties. For example, both yellow fever virus (YFV; flavivirus) and SIV (retrovirus) might persist together in their natural hosts sooty mangabeys (Woodall, 1968), which show tolerance to these viruses by significantly reducing the IFN-α level (Mandl et al., 2011). Mosquito host A. aegypti is also known to tolerate both dengue (flavivirus) and chikungunya (alphavirus) virus (CHIKV) (Kaur et al., 2018). Although genetic exchanges between such distinct virus lineages might appear far-fetched at present due to a lack of empirical support, scant evidence exists from some environmental isolates (Diemer and Stedman, 2012). For example, viral metagenomic sequences derived from a hot, acidic lake in Lassen Volcanic National Park (USA) have revealed a single-stranded DNA virus encoding a major capsid protein, which is similar to those found only in single-stranded RNA viruses, suggesting a recombinant viral genome (Diemer and Stedman, 2012). This is puzzling because mechanisms for interviral RNA-DNA recombination are unknown (Stedman, 2015). Also, indirect support for the possibility of genetic exchanges between cohabiting distinct viral pathogens might come from a recently identified novel coronavirus (labeled as Ro-BatCoV GCCDC1) found in R. leschenaultia, which carried a functional p10 gene (involved in the formation of cell syncytia) possibly derived from a bat-isolated orthoreovirus (Huang et al., 2016). In this example, the putative inter-family heterologous recombination event between a single-stranded RNA virus (i.e., ancestral beta-coronavirus) and a double-stranded segmented RNA virus (i.e., orthoreovirus) hints at possibilities of how specific genetic events might trigger the formation of recombinant viruses in nature with potentially altered transmission potential (Huang et al., 2016). Another example is the novel bandicoot papillomatisos carcinomatosis virus type 1 (BPCV1), isolated from western barred bandicoots (Perameles bougainville), which exhibited genomic properties of both the Papillomaviridae and the Polyomaviridae family of viruses (Woodford et al., 2007). These observations (and perhaps many more that await discovery in future) indicate that genetic exchanges between diverse groups of pathogens are indeed possible in natural conditions and such possibilities might increase proportionally with the time spent together inside a tolerant host. For example, longitudinal observation of one population of Rousettus leschenaultii bats for 2 years found recombinants of RdRp (RNA-dependent RNA polymerase) and p10 genes.
Evolution of immune evasion strategies by pathogens

Pathogens, especially viruses, can evolve much faster than their hosts, presenting numerous mechanisms to avoid immune sensing (Silvestri, 2009). SIV, for example, can rapidly produce variants that can escape cytotoxic T lymphocytes of their natural host sooty mangabeys (Kaur et al., 2001). A certain allelic variant of the Nef gene product from SIV downregulates the CD3-T-cell receptor complex from infected CD4+ T cells, suggesting the ability to block the counteractive immune responses and maintain the viral persistence (Schindler et al., 2006). This perhaps also exemplifies how pathogens might adapt to bypass host immunity, promoting a tolerance-like response to avoid harmful effects of immune activation. However, such function was lost during viral evolution in the lineage that ultimately gave rise to HIV-1. Most recently, a novel variant of SARS-CoV-2 (B.1.427/B.1.429), isolated from California (USA), was also found to harbor spike glycoprotein mutation that could reduce the neutralization effectivity of the Wuhan-1 isolate-based mRNA vaccine (McCallum et al., 2021), suggesting the possibility of new mutations aiding rapid evolution of the virus against vaccine-elicited antibodies (also see SARS-CoV-2 B.1.617.2 (Delta) variant identified in the state of Maharashtra, India, against BNT162b and ChAdOx-1 vaccines; Kemp et al., 2021).

Conversely, host-pathogen tolerogenic interactions over an evolutionary timescale might also lead to progressive loss of immune evasion mechanisms in the pathogen, potentially reducing their infectivity to future hosts. Perhaps, one of the best-documented examples includes Myxoma virus (MYXV), which is highly pathogenic to European rabbits, with a case fatality rate close to 100% (Peng et al., 2016). The same virus lost its virulence by 50–70% after being introduced in Australia to counter their invasive rabbit populations. During this coevolution, the Australian isolate of MYXV suffered a loss of function mutation in their protein M156, which is critically required to counter host antiviral protein kinase R (Peng et al., 2016). In contrast, SIV is known to retain its infectivity across species even after a long-term transgenerational association with experimentally inoculated monkey hosts, as noted in the case of cross-infection from laboratory macaques to humans (Khabbaz et al., 1994). More studies are perhaps required to test these diverse pathogen-specific outcomes vis-a-vis zoonotic transmission.

Supporting evidence for tolerance and pathogen prevalence from vaccination studies

Finally, recent vaccination studies in poultry birds can also offer some important clues on how tolerance can in principle influence the pathogen persistence and diversity. This is particularly true for vaccines that operate by reducing the disease symptoms (i.e., leaky vaccines), rather than preventing the infection, pathogen replication, and transmission (Gandon et al., 2001; Read et al., 2015). Infection outcomes in these vaccinated hosts largely resemble several features of tolerance where pathogens do not cause disease despite an extended infectious period (Mackinnon et al., 2008), but become progressively more virulent to other nonvaccinated hosts (compare with Horns and Hood, 2012 model). For example, more virulent strains of Marek’s disease virus appeared, persisted, and were transmitted among chickens when they were vaccinated (Read et al., 2015). Here, the ability to withstand infection via leaky vaccines perhaps provided the ideal ecological conditions that facilitated modified viral strains to emerge, persist, circulate, and transmit effectively, which otherwise would have been lethal for the chicken host to carry.

Another example is live vaccination with attenuated strains of porcine reproductive and respiratory syndrome virus (PRRSV), which prevents the development of disease symptoms in pigs but does not protect them against contracting the infection (Nan et al., 2017). In fact, the application of live vaccines might result in PRRSV variants that cause clinical severity and elevated viremia in the naïve inoculated pigs, suggesting a reversal of virulence level (Jiang et al., 2015; Liu et al., 2018). Although mechanisms are unknown (Zhou et al., 2021), tolerance after vaccination could facilitate genetic diversification of the circulating viruses, enabling them to evolve newer immune evasion strategies and revive virulence. Indeed, a recent study on chicken vaccinated against infectious bronchitis virus (IBV) has detected selection pressure, resulting in the diversification of viral coat proteins (Franzo et al., 2019). This provides a plausible evolutionary mechanism of producing newer vaccine escape variants as well as variants with wider infectivity to new hosts (Franzo et al., 2019). Future studies...
should thus compare and analyze these different vaccination contexts to verify whether they create likely niches for persistent pathogens and genetic alterations to create new emerging variants – some of them might just be competent enough to cause spillover by infecting new hosts more successfully. We also speculate that underlying mechanisms might be different from that of tolerance achieved via reducing host immune responses, selecting for either loss of immune evasion strategies or lower infectivity of pathogens (discussed above). However, there are no experiments to test whether and how these potentially different tolerance mechanisms might produce contrasting effects on pathogen evolution and emergence.

An integrated immune-centric experimental paradigm

Host immune strategies, ecology, and pathogen prevalence all play instrumental roles in facilitating spillover, but studying them in isolation is far from ideal given the complex interactions that are involved therein. Costly immune responses might evolve to act at suboptimal levels in the wild due to constraints from available resources and physiological states (Viney and Riley, 2017). Although large-scale research focusing on model host-pathogen interactions has mostly studied molecular aspects, there is a growing consensus that in the wild, host ecology, life-history, and physiological constraints are important mediators of optimal immune strategies, infection risk, and myriad infection outcomes (Graham, 2021; Restif and Graham, 2015). An integrated approach is thus needed where they should be jointly studied to explain the patterns and processes of pathogen prevalence and infection outcomes in the wild. Below, we suggest a few interrelated research foci that can be combined with traditional disease surveillance programs, aiding biological risk assessment of future EIDs (see Figure 3 for a brief outline of the suggested experimental paradigm).

Suggestion 1: identify the plausible ecological niches for emerging infections

Our understanding of emerging diseases from natural reservoirs has increased substantially over the past two decades (White and Razgour, 2020), but unfortunately, this knowledge is limited to a handful of species under scrutiny from specific geographic locations. For example, rodents and bats are of special interest from a human disease perspective since they harbor about 60 and 30% of known zoonotic viruses, respectively (Johnson et al., 2020). However, it is often overlooked that they also commonly utilize landscapes frequently occupied by other species, including humans and domestic animals (Morand et al., 2014), increasing the possibility of exchanging microbes at multiple interfaces of species interactions. They might not always cause disease outbreaks, with most of them being benign transfers, but they can help to estimate the risk of the background spillover rate among hosts of different taxa (Flores et al., 2017; Gao et al., 2016).

Transmission dynamics might also be contingent on intermediate hosts and vector populations (Plowright et al., 2017). Understanding pathogen persistence and release from intermediate hosts can lead to unearthing important bottleneck events during the emergence of novel infectious diseases (Cui et al., 2017). Hence, in addition to traditional practices of selectively obtaining data from only a very few overtly represented reservoir species from any location (Watsa, 2020), future efforts can be directed towards continuous monitoring of pathogen abundance and strain diversity across different interacting species occupying the same niche, including potential reservoirs, intermediate and human hosts. Further, it is important to collect such data simultaneously from various landscapes with altered species interactions and community composition because each location provides unique ecological niche catering to diverse host-pathogen interactions. More information across different locations can eventually motivate powerful comparative analyses to uncover novel associations between new host species (or populations) and future zoonotic routes.

Long-term tracking of pathogens and disease with altered species interactions is perhaps most relevant for rapid land-use changes in recent decades (Guo et al., 2019) – deforestation and the resulting loss of biodiversity have already been identified as one of the major driving forces influencing the risk of disease spread from animals to humans (Daszak et al., 2000; Gibb et al., 2020; Patz et al., 2008). Some of the ecological mechanisms influencing disease transmission in anthropogenically modified habitats are certainly the changes in the niche of the interacting species (host/vector/pathogen), their altered behavior, distribution in space, and animal movement patterns (Gottdenker
The relative importance of one or more of these mechanisms in explaining the response to land-use changes is likely to vary across regions. For instance, South Asia has undergone large-scale land conversions at alarming rates, losing approximately 30% of its forest land (Sudhakar Reddy et al., 2018) and, hence, can be the hotspot for EIDs (Coker et al., 2011). We thus strongly recommend a long-term disease surveillance program where multiple such regions should be first identified and then jointly analyzed to understand whether and how altered species interactions are responsible for pathogen abundance and occurrence in different animal hosts across ecosystems. This should be closely followed by tracking how they in turn influence the pathogen communities (with zoonotic potential) found in overlapping human populations.

We note that PREDICT, an epidemiological research program funded by the United States Agency for International Development (USAID), was operational until recently to identify broad patterns of emerging pathogens with pandemic potential in geographical regions that are disease hotspots such...
as the Republic of Congo, China, Egypt, India, and Malaysia (Karesh, 2011). However, after a decade from its inception, the PREDICT program ended a few weeks before the SARS-CoV-2 pandemic began. In the spirit of PREDICT, there are now several other global surveillance projects that aim to identify novel pathogens before they emerge in human populations. The Global Virome project focuses on the discovery of zoonotic viruses in the hope to prevent the next pandemic (https://www.globalvirome-project.org; Carroll et al., 2018). Similarly, two other programs focus on cataloguing the diversity of life on earth (including pathogens and parasites). These include BIOSCAN (https://ibol.org/projects/bioscan), the extension of the International Barcode of Life Program (Hobern, 2021), and the Earth BioGenome Project (https://www.earthbiogenome.org; Lewin et al., 2018). Programs, like the ones cited above, have generated a lot of basic knowledge on mammalian pathogens, especially viruses, and have aided the recent pandemic effort by understanding potential spillover pathways, as well as the ability to rapidly isolate and classify SARS-CoV-2 (Carlson, 2020). However, it is critical to remember that spillover events that spark pandemics are inherently stochastic, and there continues to be doubt on the direct abilities of programs, like PREDICT, to prevent future pandemics (Holmes et al., 2018). Thus, funding of these programs should not detract from the need for increased funding to monitor at-risk human populations, such as those living in areas of high spillover risk (Holmes et al., 2018). Additionally, there is an urgent need to support and expand networks that aim to rapidly disseminate epidemiological information such as the WHO’s Global Outbreak Alert and Response Network (GOARN), Global Initiative on Sharing All Influenza Data (GISAID), and preprint servers such as Virological (http://virological.org). Finally, proactive programs aimed at pandemic prevention also critically need more spatial and temporal information describing key changes in ecological communities (e.g., biotic homogenization) and environmental parameters (e.g., global climate change) to better understand why circulation and transmission risk of zoonotic pathogens might vary across ecosystems. A recent web-based application ‘SpillOver’ is particularly useful to gain some of these insights (Grange et al., 2021). In addition to information on viruses (e.g., virulence, breadth of viral infectivity), hosts (e.g., genetic relatedness of hosts to humans, the severity of disease in humans), and the environment (e.g., deforestation, land use), the application also considers other ancillary factors such as frequency and intimacy of human interactions with wild and domestic animals to calculate the spillover risk of 887 wildlife viruses and assess their pandemic potential. We hope that more data on host-pathogen communities and their myriad interactions and effects at the backdrop of various human interventions will further improve its location-specific predictive power.

Suggestion 2: explain the observed variations in pathogen prevalence data

An integrated program to catalog pathogens across species, populations, and locations will prepare a unique stage to subsequently ask more mechanistic questions; for example, explaining the macro-scale structural variations, using diverse metrics of host immunological, ecological, and physiological parameters. However, multiple challenges need to be overcome to conduct any meaningful analyses. Below, we describe the indispensability of accepting the challenges and testing the natural variation in immune strategies and their complex interplay with life-history to explain EID prevalence and emergence.

A. Role of immunity and tolerance

While the role of host immune responses in shaping heterogeneous infection outcomes (Duneau et al., 2017) and pathogen evolution (Retel et al., 2019) is unquestionable, their importance in driving naturally occurring variations in pathogen prevalence should gain more attention. Tracing the link between variations in inflammatory responses, tolerance, pathogen abundance, and diversity can provide insightful evidence about how the infection outcomes and their downstream effects on pathogen transmission vary across reservoir species populations. However, estimating zoonotic pathogen load in wild reservoirs and linking them to changes in their fitness proxies (i.e., tolerance; changes in the slope of fitness-by-pathogen load; Ayres and Schneider, 2012) can be notoriously difficult because of poor field understanding of their biology and lack of controlled experimental paradigm. Besides, it is often not feasible to use similar fitness parameters to measure tolerance across species and pathogens due to differences in the mode of pathogenesis and physiological processes involved. Conversely, tolerance is easier to estimate where pathogen-specific impacts on measurable
host fitness parameters are known. For example, a recent study standardized skin lesion prevention efficacy as an important fitness proxy to estimate tolerance in salamander species to a pathogen Batrachochytrium salamandrivorans that usually infects amphibian skins (Wilber et al., 2021). In contrast, another study used the extent of fin damage caused by ectoparasite Tracheiastes polycolpus (which feeds specifically on and destroys fins) as a proxy in a wild population of cyprinid freshwater fish (Leuciscus bursigalensis) (Mázé-Guilmò et al., 2014). In Atlantic salmon (Salmo salar), tolerance was quantified by assessing eye cataract formation as a degree of pathology against increasing burden of eye fluke Diplostomum pseudospathaceum (Klemme et al., 2020). All these examples suggest that we need to design long-term studies to first understand the basic life history of key reservoir species in the wild to standardize fitness measurements and observe their response to pathogens of significant zoonotic interests (e.g., counting number of circulating hemocytes, antibody titers). This will enable us to understand the actual ecological role of zoonotic infections and disease manifestation in wild host populations. Moreover, long-term studies are also important to reveal how selection acts on the host immune system against pathogens of interest. For instance, Sparks and coworkers collected data for 26 years from wild Soay sheep (Ovis aries) populations to distinguish how natural selection acts separately on three functionally distinct isotypes of antibodies (IgA, IgE, and IgG) against a prevalent nematode parasite Teladorsagia circumcincta (Sparks et al., 2018). Future studies might consider comparable frameworks to reveal the mechanistic basis of how immune system might evolve with pathogen burden and is linked to fitness effects in reservoir hosts against zoonotic pathogens.

A few earlier studies have successfully looked into tolerance by estimating fitness traits such as body mass, standing pathogen load, lifespan, and number of offspring produced per year in rodent populations (Jackson et al., 2014; Rohfritsch et al., 2018; Schneider, 2011), which can be replicated in future as well. A recent study with natural populations of Anolis sagrei lizards also used body condition, locomotor performance, and survival to the end of the breeding season as a function of infection with Plasmodium parasites (Bonneaud et al., 2017). However, rodents can be used as a more relevant model species to link tolerance with emerging infections as they are one of the largest disease reservoirs (Gravinatti et al., 2020), ubiquitously found in all ecosystems. Also, the immune system of several highly abundant rodent species such as Rattus rattus or Mus musculus is very well-characterized (Abolins et al., 2017; Viney et al., 2015), providing the opportunity to correlate known immune parameters against zoonotic pathogens with measurable fitness traits. Future studies can also design these assays in various ecosystems based on previous rodent experiments, where both cross-sectional and longitudinal sampling using the capture-recapture method were implemented to provide stronger causal inferences (Jackson et al., 2014).

Obtaining reliable molecular biomarkers of immunity in wild reservoirs is also important to provide direct evidence for how inflammatory responses might vary across spatial and temporal scales and allow some hosts to tolerate the pathogen, while others cannot (Burgan et al., 2018; Jackson et al., 2014). Indeed, a major challenge is the lack of reagents such as monoclonal antibodies for most wild species, but an increase in the number of fully sequenced genomes and de novo transcriptome assemblages of different reservoir species in the ecological community can overcome these limitations. This information can enable us to compare the immune-related transcripts and gene expression patterns to produce cross-reactive recombinant proteins for protein-based assays across taxa (Flies et al., 2020b). Indeed, recent efforts have also been successful to sequence whole genomes of different bat species (Jebb et al., 2020). The Bat1k genome consortium aims to sequence and annotate chromosome-level genome assemblies of all living bat species to probe genetic mechanisms underlying their unique adaptations to zoonotic viruses (Teeling et al., 2018). Additionally, developing standardized sets of reagents for rapid serological assays of immunoglobulins and key cell types such as resident memory T cells that can react across species can also be extremely helpful to track how species interactions within an ecological niche can influence the possibility of shared zoonotic pathogen pools (Flies et al., 2020b).

B. Complex interplay with life history
Host immune strategies and disease tolerance might explain pathogen abundance and strain diversity, but they are unlikely to work in isolation without a whole organismal and physiological perspective. This is primarily because immune strategies are contingent on diverse life-history parameters such
Table 1. Plausible effects of different life-history traits on immune responses and tolerance. Although resource availability and nutrition are not life-history traits, we listed them as they impact body condition and fitness (Huang et al., 2013). ‘↑’ denotes increase in tolerance while ‘↓’ denotes decrease in tolerance.

| Traits                  | Plausible effects on infection and immunity                                                                 | Reference                  | Predicted role in tolerance |
|-------------------------|-------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------------|
| Reproduction            | Higher investment in reproductive output trades-off with immune responses                                 | Short et al., 2012         | Higher reproduction↑         |
| Mating effort           | Increased mating activity leads to immune suppression                                                      | Rolff and Siva-Jothy, 2002 | Increased mating effort↑     |
| Pace of life            | Fast pace of life reduces investment in immunity and allocate more resources to early-sexual maturity and reproductive output | Previtali et al., 2012     | Animals with fast pace of life↑ |
| Sex                     | Option 1: Males invest less in immunity due to high intra-sexual competition for females and variation in reproductive success | Bateman, 1948; Zuk and Stoehr, 2002 | Males↑*                     |
|                         | Option 2: Males disperse more and hence, are exposed to increasing number of (diverse) pathogens          | Streicker et al., 2016     | Males↑                      |
|                         | Option 3: Organ-specific localization and impacts of pathogens across sexes, e.g., pathogens that could infect and colonize only ovary might show female-specific pathology | Brandt and Schneider, 2007 | Males↑                      |
| Age                     | Younger individuals maximize their reproduction by minimizing investment in immune activation and pathogen clearance, thereby avoiding fitness-reducing immunopathological consequences | Khan et al., 2017a; Medzhitov et al., 2012 | Younger individuals↑         |
| Starvation/availability of resource | Option 1: Organisms invest less in immune defenses when deprived of resources | Stucki et al., 2019        | Starving individuals↑        |
|                         | Option 2: Well-fed individuals can withstand the effects of pathogens without clearing them because of their better body condition | Knutie et al., 2016        | Well-fed individuals↑        |
| Nutrition               | Option 1: Access to a proteinaceous diet might boost the immune system and pathogen clearance ability      | Povey et al., 2009         | Higher protein content↓      |
|                         | Option 2: Access to a proteinaceous diet might allow hosts to compensate for the costs of harboring pathogens | Knutie et al., 2017        | Higher protein content↑      |

*Also see contrasting examples in Jarefors et al., 2006 or Cousineau and Alizon, 2014; females invest more in anti-inflammatory responses which might increase their tolerance.

as age, sex, reproductive status, or body condition (Nystrand and Dowling, 2020; Poirier, 2019; Smith et al., 2019). A previous meta-analysis by Han and colleagues (Han et al., 2016) has identified a diverse array of life-history traits such as gestation length, longevity, group size, mating system, offspring per year, and age of sexual maturity that makes certain species ideal as zoonotic reservoir hosts. However, these patterns make more sense if analyzed in terms of how hosts at a particular life-history condition could maintain pathogens by altering their so-called combative and counteractive immune strategies (Valenzuela-Sánchez et al., 2021; see Table 1 for a few examples highlighting life-history traits and their proposed role in immunity and tolerance).

Males are more likely to harbor a greater diversity of pathogens compared to females due to their increased propensity to disperse, exposing them to encounter more pathogens (Streicker et al., 2016). Also, host systems that are sexually dimorphic in immunity and infection outcomes can provide the pathogen with two selectively distinct environments (Gipson and Hall, 2016; Khan and Prasad, 2011), imposing far-reaching impacts on disease transmission, especially in populations with skewed sex ratios. Life-history traits such as lifespan, sexual maturity, and reproductive output that make certain species ideal for natural reservoirs (Han et al., 2016) can perhaps be mediated via resource allocation trade-offs (Schwenke et al., 2016), where limiting the activation of costly immune responses might promote other fitness traits and favor pathogen tolerance. For example, several host species like rodents that thrive in human-dominated landscapes
usually have a fast pace of life, reducing investment in immunity and thereby harboring more pathogens at any given timepoint (Gibb et al., 2020) – early maturity and high early-reproductive output (e.g., increased reproduction at a young age; see Medzhitov et al., 2012) can trade-off with immune responses allowing rodents to become competent natural reservoirs for zoonotic pathogens (Ostfeld et al., 2014). In nature, frequently encountered stressful environments such as poor nutrition can also have severe impacts on immune investment and pathogen tolerance (Wang et al., 2016). For example, burying beetle (Nicrophorus vespilloides) feeding on a low protein diet showed increased tolerance to Photorhabdus luminescens (Miller and Cotter, 2018). Another study on Cuban tree frog (Osteopilus septentrionalis), however, found increased tolerance to skin penetrating nematode Aplectana sp. when maintained on proteinaceous insect diets (Knutie et al., 2017), suggesting that impacts of nutrition on tolerance are perhaps host- and pathogen-specific. Nonetheless, considering these multifaceted implications of host physiology and various life-history traits in immunity and disease tolerance, it is imperative to analyze the role of these parameters in explaining pathogen prevalence data collected during disease surveillance. Different life-history traits can interact closely to drive the level of and pathogen prevalence. For instance, in addition to dispersal (discussed above; Streicker et al., 2016), higher pathogen burden in males can be explained by their lower investment in immunity as they typically experience stronger intra-sexual competition and a greater variance in reproductive success (Bateman, 1948; Zuk and Stoehr, 2002). As implicated above, even age, sexual maturity, pace-of-life, or nutritional status might manifest their effects on immunity and tolerance by altering reproductive investments. Sexually dimorphic immune investment, causing sex-specific divergence in tolerance and pathogen prevalence, may evolve as a function of intersexual resource competition (Li and Kokko, 2019) or mating strategies (Bagchi et al., 2021). We certainly need future studies to explore these intimate interactions and pinpoint complex life-history and physiological features of reservoirs that can be attributed to their disease-carrying ability.

**Suggestion 3: identify the host-pathogen coevolutionary dynamics to predict emerging infections**

Analyzing changes in genes involved in host-pathogen interactions can generate crucial insights about their association over an evolutionary timescale (Woolhouse et al., 2002). For instance, virulence genes involved in continuous host-pathogen arms race tend to display positive selection (dN/dS > 1) in the codons that are involved in the interaction sites between the virus and host cell receptor (Daugherty and Malik, 2012; Meyerson and Sawyer, 2011). Indeed, host cell receptors for viruses like HIV (cluster of differentiation 4), filovirus (Niemann-Pick C1), and several coronaviruses (angiotensin-converting enzyme 2) have been shown to undergo positive selection across different mammalian orders (Pontremoli et al., 2016; Wang et al., 2020). SIV envelope protein binding domain of CD4 receptor (D1 domain) in many African primate species has undergone diversification in the coding sequence (Zhang et al., 2008). The amino acid replacements in the D1 domain can prevent viral envelope glycoprotein (Env)-CD4-mediated cell entry in multiple African primate species, protecting them from SIV infection (Zhang et al., 2008). A recent study has further revealed that diversification of CD4 receptor, with as many as 11 coding variants in Moustached monkey Cercopithecus cephus, might be under balancing selection as an outcome of the long-term coevolutionary arms-race with primate lentiviruses (Russell et al., 2021). Quantifying selection pressures acting at various host receptor-pathogen interfaces by calculating respective dN/dS ratios (Yang and Bielawski, 2000) can thus help us in unearthing evidence of the evolutionary history of exposure; for example, (1) high or low degree of filovirus exposure to natural reservoir bat vs. novel human hosts respectively; or (2) genomic signatures left by pathogenic primate lentiviruses in susceptible primate species vs. other long-term SIV-infected species such as sooty mangabeys evolving specific mechanisms to avoid the disease progression (Russell et al., 2021). The consequences of long-term positive selection on pathogens might also transcend into evolved variants with new antigenic properties and possible expansion of the host range (Bedi et al., 2013). Indeed, in the case of SARS outbreak in 2002, selection on the spike gene of SARS-CoV was positively correlated with its spillover from palm civets to humans (Chinese SARS Molecular Epidemiology Consortium, 2004). The binding affinity of the virus spike protein towards human ACE2 changed from low to high due to mutations in two critical amino acids, turning it into a pandemic strain (Chinese SARS Molecular Epidemiology Consortium, 2004).
Levels of pathogen sequence divergence can accelerate more with increased polymorphism of host receptors (Gupta et al., 2009; Meyerson and Sawyer, 2011; Warren et al., 2019), allowing pathogens to infect and adapt to another host more effectively (Daugherty and Malik, 2012). For instance, a recent study that analyzed ACE2 receptors in Chinese horseshoe bats (Rhinolophus sinicus) found multiple such highly polymorphic sites in the receptor regions, which interacts with the spike proteins of a coronavirus isolated from the same species of bats named as SARSr-CoV (severe acute respiratory syndrome coronavirus isolated from R. sinicus; Guo et al., 2020). As expected, binding affinities of SARSr-CoV to these polymorphic receptors varied widely, making some cells more susceptible to viral entry than others. However, the most interesting aspect of their study was that, when tested upon human cell lines, some of these SARSr-CoV strains even showed higher binding affinity to human ACE2 compared to that of R. sinicus, hinting at their potential to cause spillover in overlapping human populations (Guo et al., 2020). Given the direct implications of these results in spillover and human health, we suggest the need for more such analyses to uncover the coevolutionary outcomes of pathogens from the diverse host interface (e.g., reservoirs vs. other host species), both at the spatial as well as the temporal scales.

Future studies can also test whether and how coevolving viral pathogens can maintain genetic polymorphism for adaptation to the host immune environment. Probing signatures of coevolution in accessory proteins that target host-associated restriction factors can aid understanding of the complex interplay between immune defense and viral adaptations. Indeed, the importance of such evolutionary processes has been implicated in previous studies where modified strains of HIV (simian tropic HIV-1 strain; stHIV-1) rapidly evolved to antagonize host restriction factor tetherin by acquiring mutations in the accessory protein Vpu within merely four passages through an atypical HIV-1 host species pigtailed macaques (Macaca nemestrina; Hatzioannou et al., 2014). There are several other accessory genes as well such as Nef, Vif, and Vpr that have evolved in lentiviruses to counteract host antiviral immune responses (Sauter and Kirchhoff, 2018). Hence, in addition to finding links between host immune strategies (resistance vs. tolerance), life-history, and pathogen prevalence, revealing coevolutionary dynamics and resulting genetic diversification of circulating pathogens (i.e., key molecules involved in host entry, infectivity, and virulence) can greatly advance our understanding of their range expansion via spillover.

**Suggestion 4: set up controlled proof-of-principle laboratory coevolution studies to test hypotheses generated in the wild and provide mechanistic insights**

It is important to note that due to the involvement of a multitude of factors ranging from genetics to environmental variations influencing animal populations, evaluating disease tolerance and pathogen spillover can be complicated in the wild. Data from field experiments can certainly provide information about larger patterns and processes such as heterogeneity in immune responses and genetic diversity in circulating pathogen strains, but creating a controlled empirical paradigm is perhaps necessary to generate more mechanistic insights into the actual micro-evolutionary processes. Finding greater pathogen diversity and prevalence in reservoir hosts with lower inflammatory responses, reduced rate of fitness loss, and increased polymorphism in pathogen receptor sites might indicate a potential correlation between coevolution, tolerance, and diverse zoonotic pathogen pool, but the causal link is still difficult to establish. Using common garden experimental setups that allow rearing and maintenance of well-characterized focal organisms under study in their semi-natural environmental conditions (e.g., large field enclosures for wild mice) can help us to partially overcome the uncertainties associated with quantifying parasite burden and estimating fitness traits in the wild (Barrett et al., 2019; Klemme et al., 2020).

Yet it might be challenging to answer some of the most fundamental questions, such as do hosts actually evolve tolerance to their natural pathogens? If so, how do we track such evolutionary processes? Besides gathering clues from comparative studies using various host populations, laboratory experimental evolution using tractable animal models (with known biology and genomic information) can be an excellent alternative to test these possibilities (Khan et al., 2017b; Masri et al., 2013; Prasad and Joshi, 2003). They can enable us to directly track host-pathogen dynamics and test diverse hypotheses on the evolution of host tolerance, genetic diversifications of pathogens, and spillover risk to overlapping susceptible host populations. Owing to rapid generation time and
easy maintenance, insect hosts, in particular, provide an excellent system to conduct such long-term evolution experiments (e.g., see Ford et al., 2020; Khan et al., 2017b; Mukherjee et al., 2019; but also see Kohl et al., 2016 for study in voles). While in principle any well-characterized insect model, with known biology and genetic information, can be used to test these basic hypotheses, mosquito hosts can be particularly useful both for the fundamental discovery as well as their direct relevance to human health (Huang et al., 2019). For example, filarial infections that exert strong selection pressure in mosquito hosts by inducing high mortality can be a valuable resource to test whether fitness costs are minimized by evolving tolerance (Aliota et al., 2010; Bartholomay, 2014). Experimental evolution studies can also be combined with a comparative dataset where multiple wild-caught mosquito populations are analyzed to quantify the natural variation in tolerance to filarial worms, followed by probing their underlying immune profiles. Subsequently, populations showing lower tolerance can be identified and subjected to repeated exposure to filarial infection across generations to test whether the level of tolerance can be further increased by modulating inflammatory responses. Such an integrated empirical framework might help in establishing the proposed causal link between coevolutionary history and pathogen tolerance (see Figure 4).

A similar experimental paradigm can also be used to test whether shared evolutionary history is responsible for tolerance in the vector hosts against their natural pathogens. For example, mosquito species Armigeres subalbatus is a natural vector for the zoonotic filarial worm Brugia pahangi whom they can tolerate, but not the morphologically and biologically similar pathogen Brugia malayi (Aliota et al., 2010; Aliota et al., 2007), which is perhaps not as prevalent as B. pahangi in the mosquito hosts (Muslim et al., 2013). In fact, mosquito hosts resist B. malayi infection using costly immune responses (Aliota et al., 2010; Aliota et al., 2007). Can long-term coevolution reverse such effects of B. malayi infection? By experimentally imposing long-term selection with the new pathogen B. malayi, we can verify the causal connection between the length of coevolutionary history and the level of host tolerance and parasite evolution. Subsequently, genetic analyses can uncover the mechanistic basis of adaptive changes in host immunity (e.g., possible modulation of costly inflammatory responses; Märkle et al., 2021) and pathogen replication and transmission potential (Siva-Jothy and Vale, 2021).
Laboratory evolution studies can also be implemented to track the evolutionary origin of established molecular mechanisms underlying tolerance strategies adopted by vector hosts. For example, both *A. albopictus* and *A. aegypti* can rapidly synthesize viral-derived DNA (vDNA), which is crucial for their tolerance and survival against chikungunya virus and dengue virus, respectively (Goic et al., 2016). How did such mechanisms evolve? A possible empirical framework is to (1) collect naturally isolated *Aedes* populations lacking (or with inherently lower) viral tolerance; (2) impose long-term viral selection to directly test whether stronger tolerance is correlated with increased vDNA synthesis; and (3) finally, test whether such evolved tolerance can be reversed by reducing vDNA synthesis (using reverse genetics) to verify its functional role (see Goic et al., 2016). Since previous experiments already demonstrated the role of tolerance in increasing the transmission intensity and vectorial capacity in mosquitoes (Dharmarajan et al., 2019), experiments showing direct evolution of parasite tolerance and infectivity in important vectors will make crucial contributions to public health (Lambrechts and Saleh, 2019).

### Conclusion and further implications for public health

In closing, as disease-causing pathogens from wild animals are emerging at an unprecedented rate across the globe, we must acknowledge that our understanding of specific ecological interactions and adaptive features of reservoir hosts is still at a nascent stage. A few theoretical models and experiments have provided broader insights into specific immune strategies to cater persistence of zoonotic pathogens (Alexander et al., 2012; Brook et al., 2020; White et al., 2018), but their oversimplistic assumptions might have limited inferential value in nature. To fill this gap, we have compiled a range of direct and indirect evidence of tolerance that can potentially explain the pathogen prevalence across host-pathogen systems, indicating its wider relevance to disease spread and spillover. However, despite the conceptual appeal, predictions based on the tolerance of reservoir hosts in catalyzing emerging infections still lack empirical rigor. There are no experiments that have thoroughly verified the whole process; that is, evolution of pathogen tolerance in reservoir animals to spillover. Recent analyses appear promising as they reveal the genetic basis differentiating the pathogen resistance from tolerance in critical human diseases such as HIV, where a high viral load often coincides with minimal disease progression as a feature of tolerance (Regoes et al., 2014). Also, there are experiments with bacteriophages that have confirmed that genetic variations are indeed required for viral emergence and host expansion (Dennehy et al., 2010). Still, targeted studies in natural reservoirs are needed to jointly probe the whole spectrum of tolerance to pathogen emergence, validating their cascading impacts on the spillover.

To this end, an integrated immune-centric understanding of naturally occurring variable infection outcomes across different host-pathogen systems and their specific ecological contexts, life-history, and evolutionary implications can be crucial. Systematic verification of the proposed links between pathogen prevalence, pathogen diversity, and host tolerance across a range of ecological contexts is needed, followed by deeper evolutionary insights into the maintenance of latent pathogen reservoirs and conditions that trigger spillover events. We believe that a hypothesis-driven experimental framework based on previous theoretical models is timely and will conceptually motivate a wide range of biologists to adopt a proactive disease surveillance program complemented with deeper ecological, evolutionary, and immunological thinking. Finally, we expect that our review will not only be relevant to the present crisis created by pandemic and emerging infections, but it will also provide a newer understanding of other important aspects of public health research such as infectious disease control (e.g., consequences of disease tolerance via vaccination) and the dynamics of noninfectious diseases (e.g., increased risk autoimmune disorders in geographical regions where improved hygiene has reduced pathogen burden; Bach, 2018).

### Acknowledgements

We are grateful to Basabi Bagchi, Saubhik Sarkar, Biswajit Shit, Devshuvam Banerjee, Manasven Raina, and Shashwat Goyal for feedback on the manuscript. Figures were designed in the Biorender platform.
Additional information

### Funding

| Funder                        | Grant reference number | Author        |
|-------------------------------|------------------------|---------------|
| U.S. Department of Energy     | DE-EM0004391           | Guha Dharmarajan |
| Ashoka University             |                        | Srijan Seal, Imroze Khan |
| Wellcome Trust/DBT India Alliance | IA/I/20/I/504930   | Srijan Seal, Imroze Khan |

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

### Author contributions

Srijan Seal, Conceptualization, Writing – original draft; Guha Dharmarajan, Writing - review and editing; Imroze Khan, Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing - review and editing

### Author ORCIDs

Srijan Seal [http://orcid.org/0000-0003-4610-3964](http://orcid.org/0000-0003-4610-3964)
Imroze Khan [http://orcid.org/0000-0002-8793-5081](http://orcid.org/0000-0002-8793-5081)

### References

Abolins S, King EC, Lazarou L, Weldon L, Hughes L, Drescher P, Raynes JG, Hafalla JCR, Viney ME, Riley EM. 2017. The comparative Immunology of wild and laboratory mice, *Mus musculus domesticus*. *Nature Communications* 8: 14811. DOI: [https://doi.org/10.1038/ncomms14811](https://doi.org/10.1038/ncomms14811), PMID: 28466840

Adelman JS, Kirkpatrick L, Grodio JL, Hawley DM. 2013. House finch populations differ in early inflammatory signaling and pathogen tolerance at the peak of *Mycoplasma gallisepticum* infection. *The American Naturalist* 181: 674–689. DOI: [https://doi.org/10.1086/670024](https://doi.org/10.1086/670024), PMID: 23594550

Adelman JS, Hawley DM. 2017. Tolerance of infection: A role for animal behavior, potential immune mechanisms, and consequences for parasite transmission. *Hormones and Behavior* 88: 79–86. DOI: [https://doi.org/10.1016/j.yhbeh.2016.10.013](https://doi.org/10.1016/j.yhbeh.2016.10.013), PMID: 27984034

Ahn M, Cui J, Irving AT, Wang LF. 2016. Unique loss of the pyhin gene family in bats amongst mammals: Implications for inflammasome sensing. *Scientific Reports* 6: 21722. DOI: [https://doi.org/10.1038/srep21722](https://doi.org/10.1038/srep21722), PMID: 26906452

Ahn M, Anderson DE, Zhang Q, Tan CW, Luko K, Wen M, Chia WN, Mani S, Wang LC, Ng JHJ, Sobota RM, Duteretre CA, Ginhoux F, Shi ZL, Irving AT, Wang LF. 2019. Dampered nlrp3-mediated inflammation in bats and implications for a special viral reservoir host. *Nature Microbiology* 4: 789–799. DOI: [https://doi.org/10.1038/s41564-019-0371-3](https://doi.org/10.1038/s41564-019-0371-3), PMID: 30804542

Alexander KA, Lewis BL, Marathe M, Eubank S, Blackburn JK. 2012. Modeling of wildlife-associated zoonoses: Applications and caveats. *Vector Borne and Zoonotic Diseases* 12: 1005–1018. DOI: [https://doi.org/10.1089/vbz.2012.0987](https://doi.org/10.1089/vbz.2012.0987), PMID: 23199265

Aliota MT, Fuchs JF, Mayhew GF, Chen CC, Christensen BM. 2007. Mosquito transcriptome changes and filarial worm resistance in *Armagos Subalbatus*. *BMC Genomics* 8: 463. DOI: [https://doi.org/10.1186/1471-2164-8-463](https://doi.org/10.1186/1471-2164-8-463), PMID: 18088420

Aliota MT, Fuchs JF, Rocheleau TA, Clark AK, Hillyer JF, Chen CC, Christensen BM. 2010. Mosquito transcriptome profiles and filarial worm susceptibility in *Armagos Subalbatus*. *PLOS Neglected Tropical Diseases* 4: e666. DOI: [https://doi.org/10.1371/journal.pntd.0000666](https://doi.org/10.1371/journal.pntd.0000666), PMID: 20421927

Allen JE, Wynn TA. 2011. Evolution of Th2 Immunity: A Rapid Repair Response to Tissue Destructive Pathogens. *PLOS Pathogens* 7: e1002003. DOI: [https://doi.org/10.1371/journal.ppat.1002003](https://doi.org/10.1371/journal.ppat.1002003), PMID: 21589986

Ansari AA, Silvestri G. 2014. Natural Hosts of SIV: Implication in AIDS. Elsevier: Academic Press, Amsterdam ; Boston.

Atkinson CT, Saili KS, Utzurrum RB, Jarvi SI. 2013. Experimental Evidence for Evolved Tolerance to Avian Malaria in a Wild Population of Low Elevation Hawai‘i ‘Amakihi (Hemignathus virens). *EcoHealth* 10: 366–375. DOI: [https://doi.org/10.1007/s10393-013-0899-2](https://doi.org/10.1007/s10393-013-0899-2), PMID: 24430825

Auten RL, Davis JM. 2009. Oxygen Toxicity and Reactive Oxygen Species: The Devil Is in the Details. *Pediatric Research* 66: 121–127. DOI: [https://doi.org/10.1203/0b013e3181a9eaf8](https://doi.org/10.1203/0b013e3181a9eaf8), PMID: 19390491

Ayres JS, Schneider DS. 2012. Tolerance of infections. *Annual Review of Immunology* 30: 271–294. DOI: [https://doi.org/10.1146/annurev-immunol-020711-075030](https://doi.org/10.1146/annurev-immunol-020711-075030), PMID: 22247700

Ayres JS. 2020. Surviving COVID-19: A disease tolerance perspective. *Science Advances* 6: eabc1518. DOI: [https://doi.org/10.1126/sciadv.abc1518](https://doi.org/10.1126/sciadv.abc1518), PMID: 32494691
Baker ML, Bailes E, Gao F, Bibollet-Ruche F, Courgnaud V, Peeters M, Marx PA, Hahn BH, Sharp PM. 2003. Hybrid origin of SIV in chimpanzees. Science 300: 1713. DOI: https://doi.org/10.1126/science.10780567, PMID: 12805540

Baker ML, Schountz T, Wang LF. 2013. Antiviral immune responses of bats: A review: Antiviral immune responses of bats. Zoonoses and Public Health 60: 104–116. DOI: https://doi.org/10.1111/j.1863-2378.2012.01528.x

Barrett RDH, Laurent S, Mallarino R, Pfeifer SP, Xu CCY, Foll M, Wakamatsu K, Duke-Cohan JS, Jensen JD, Hoekstra HE. 2019. Linking a mutation to survival in wild mice. Science 363: 499–504. DOI: https://doi.org/10.1126/science.aav3824, PMID: 30705186

Bartholomay LC. 2014. Infection barriers and responses in mosquito–filarial worm interactions. Current Opinion in Insect Science 3: 37–42. DOI: https://doi.org/10.1016/j.cois.2014.08.006, PMID: 32846673

Bateman AJ. 1948. Intra-sexual selection in Drosophila. Heredity 2: 349–368. DOI: https://doi.org/10.1038/hdy.1948.21, PMID: 18103134

Bean AGD, Bosinger SE, Vanderford TH, Paiardini M, Silvestri G. 2012. Natural SIV hosts: Showing AIDS the door. Science 335: 985–1000. DOI: https://doi.org/10.1126/science.1217550, PMID: 22403383

Bloomfield LSP, McIntosh TL, Lambin EF. 2020. Habitat fragmentation, livelihood behaviors, and contact between people and nonhuman primates in Africa. Landscape Ecology 35: 985–1000. DOI: https://doi.org/10.1007/s10980-020-00995-w

Bonneaud C, Sepil I, Wilfert L, Calcebeek R. 2017. Plasmodium infections in natural populations of Anolis sagrei reflect tolerance rather than susceptibility. Integrative and Comparative Biology 57: 352–361. DOI: https://doi.org/10.1093/icb/icx044, PMID: 28859403

Bono LM, Gensel CL, Pfennig DW, Burch CL. 2013. Competition and the origins of novelty: Experimental evolution of niche-width expansion in a virus. Biology Letters 9: 20120616. DOI: https://doi.org/10.1098/rsbl.2012.0616, PMID: 23075527

Brandt SM, Schneider DS. 2007. Bacterial infection of fly ovaries reduces egg production and induces local hemocyte activation. Developmental and Comparative Immunology 31: 1121–1130. DOI: https://doi.org/10.1016/j.devco.2007.02.003, PMID: 17400292

Brock CE, Boots M, Chandran K, Dobson AP, Drosten C, Graham AL, Grenfell BT, Müller MA, Ng M, Wang LF, van Leeuwen A. 2020. Accelerated viral dynamics in bat cell lines, with implications for zoonotic emergence. Developmental and Comparative Immunology 106: 2041–2047. DOI: https://doi.org/10.1016/j.devco.2020.04.0177, PMID: 32011232

Burgan SC, Gervassi SS, Martin LB. 2018. Parasite tolerance and host competence in avian host defense to West Nile Virus. EcoHealth 15: 360–371. DOI: https://doi.org/10.1007/s10393-018-1332-7, PMID: 29569179

Burmeister AR, Lenski RE, Meyer JR. 2016. Host coevolution alters the adaptive landscape of a virus. Proceedings. Biological Sciences 283: 20161528. DOI: https://doi.org/10.1098/rspb.2016.1528, PMID: 27683370

Capparelli R, Parlati M, Iannaccione M, Roperto S, Marabelli R, Roperto F, Iannelli D. 2013. Heterogeneous shedding of Brucella abortus in milk and its effect on the control of animal brucellosis. Journal of Applied Microbiology 106: 2041–2047. DOI: https://doi.org/10.1111/j.1365-2672.2009.04177.x, PMID: 19298512

Cappuccio L, Maisse C. 2020. Infection of mammals and mosquitoes by alphaviruses: Involvement of cell death. Journal of Applied Microbiology 128: 20161528. DOI: https://doi.org/10.1111/jam.15201, PMID: 32835320

Carroll D, Daszak P, Wolfe ND, Gao GF, Morley CM, Morzaria S, Pablos-Méndez A, Tomori O, Mazet JAK. 2018. The global Virome Project. Science 359: 872–874. DOI: https://doi.org/10.1126/science.aap7463, PMID: 29472471

Cecilia D. 2014. Current status of dengue and chikungunya in India. WHO South-East Asia Journal of Public Health 3: 22–26. DOI: https://doi.org/10.4103/2224-3151.1206879, PMID: 28607250

Chahrourdi A, Bosinger SE, Vanderford TH, Paiardini M, Silvestri G. 2012. Natural SIV hosts: Showing AIDS the door. Science 335: 1188–1193. DOI: https://doi.org/10.1126/science.1217550, PMID: 22403383
Chakrabarti LA. 2004. The paradox of simian immunodeficiency virus infection in sooty mangabeys: Active viral replication without disease progression. *Frontiers in Bioscience* 9: 521–539. DOI: https://doi.org/10.2741/1123, PMID: 14766388

Chinese SARS Molecular Epidemiology Consortium. 2004. Molecular Evolution of the SARS Coronavirus During the Course of the SARS Epidemic in China. *Science* 303: 1666–1669. DOI: https://doi.org/10.1126/science.1092002, PMID: 14752165

Coker RJ, Hunter BM, Rudge JW, Liverani M, Hanvoravongchai P. 2011. Emerging infectious diseases in Southeast Asia: Regional challenges to control. *Lancet* 377: 599–609. DOI: https://doi.org/10.1016/S0140-6736(10)62004-1, PMID: 21269678

Compton AA, Emerman M. 2013. Convergence and divergence in the evolution of the apobec3g-vif interaction reveal ancient origins of simian immunodeficiency viruses. *PLOS Pathogens* 9: e1003135. DOI: https://doi.org/10.1371/journal.ppat.1003135, PMID: 23359341

Cousineau SV, Alizon S. 2014. Parasite evolution in response to sex-based host heterogeneity in resistance and tolerance. *Journal of Evolutionary Biology* 27: 2753–2766. DOI: https://doi.org/10.1111/jeb.12541, PMID: 25376168

Cross PC, Prosser DJ, Ramey AM, Hanks EM, Pepin KM. 2019. Confronting models with data: The challenges of estimating disease spillover. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 374: 20180435. DOI: https://doi.org/10.1098/rstb.2018.0435, PMID: 31401965

Cui J-A, Chen F, Fan S. 2017. Effect of intermediate hosts on emerging zoonoses. *Vector Borne and Zoonotic Diseases* 17: 599–609. DOI: https://doi.org/10.1089/vbz.2016.2059, PMID: 28678630

Cunningham AA, Daszak P, Wood JLN. 2017. One Health, emerging infectious diseases and wildlife: two decades of progress? *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 372: 20160167. DOI: https://doi.org/10.1098/rstb.2016.0167, PMID: 28584175

Daszak P, Cunningham AA, Hyatt AD. 2000. Emerging infectious diseases of wildlife—threats to biodiversity and human health. *Science* 287: 443–449. DOI: https://doi.org/10.1126/science.287.5452.443, PMID: 10642539

Daugherty MD, Malik HS. 2012. Rules of engagement: Molecular insights from host-virus arms races. *Annual Review of Genetics* 46: 677–700. DOI: https://doi.org/10.1146/annurev-genet-110711-155522, PMID: 23145935

Davies TJ, Pedersen AB. 2008. Phylogeny and geography predict pathogen community similarity in wild primates and humans. *Proceedings. Biological Sciences* 275: 1695–1701. DOI: https://doi.org/10.1098/rspb.2008.0284, PMID: 18445561

Day T, Gandon S, Lion S, Otto SP. 2020. On the evolutionary epidemiology of SARS-COV-2. *Current Biology* 30: R849–R857. DOI: https://doi.org/10.1016/j.cub.2020.06.031, PMID: 32750338

Dennehy JJ, Gandon S, Lion S, Otto SP. 2020. On the evolutionary epidemiology of SARS-COV-2. *Current Biology* 30: R849–R857. DOI: https://doi.org/10.1016/j.cub.2020.06.031, PMID: 32750338

Dennehy JJ, Gandon S, Lion S, Otto SP. 2020. On the evolutionary epidemiology of SARS-COV-2. *Current Biology* 30: R849–R857. DOI: https://doi.org/10.1016/j.cub.2020.06.031, PMID: 32750338

Dunne D, Ferdy JB, Revah J, Kondolf H, Ortiz GA, Lazzaro BP, Buchon N. 2017. Stochastic variation in the initial phase of bacterial infection predicts the probability of survival in *D. melanogaster*. eLife 6: e28298. DOI: https://doi.org/10.7554/eLife.28298, PMID: 29022878

Dybdaahl MF, Storfer A. 2003. Parasite local adaptation: Red Queen versus Suicide King. *Biology Direct* 7: 43–50. DOI: https://doi.org/10.1186/1745-6150-7-13, PMID: 23145935

Easterbrook JD, Klein SL. 2008. Seoul virus enhances regulatory and reduces proinflammatory responses in male Norway rats. *Journal of Medical Virology* 80: 1308–1318. DOI: https://doi.org/10.1002/jmv.21213, PMID: 18461618

Ermonval M, Baychelier F, Tordo N. 2016. What Do We Know about How Hantaviruses Interact with Their Different Hosts? *Viruses* 8: 223. DOI: https://doi.org/10.3390/v8080223, PMID: 27529272

Etienne L, Hahn BH, Sharp PM, Matsen FA, Emerman M. 2013. Gene loss and adaptation to hominids underlie the ancient origin of hiv-1. *Cell Host & Microbe* 14: 85–92. DOI: https://doi.org/10.1016/j.chom.2013.06.002, PMID: 23870316

Flies AS. 2020a. Rewilding immunology. *Science* 369: 37–38. DOI: https://doi.org/10.1126/science.abb8664, PMID: 32631885

Flies AS, Darby JM, Lennard PR, Murphy PR, Ong CEB, Pinfold TL, De Luca A, Lyons AB, Woods GM, Patchett AL. 2020b. A novel system to map protein interactions reveals evolutionarily conserved immune evasion pathways on transmissible cancers. *Science Advances* 6: eaba5031. DOI: https://doi.org/10.1126/sciadv.abas0531, PMID: 32937435

Flores BJ, Pérez-Sánchez T, Fuertes H, Sheleby-Elias J, Múzquiz JL, Jirón W, Duttmann C, Halaihel N. 2017. A cross-sectional epidemiological study of domestic animals related to human leptospirosis cases in Nicaragua. *Acta Tropica* 170: 79–84. DOI: https://doi.org/10.1016/j.actatropica.2017.02.031, PMID: 28254582
Ford SA, Albert I, Allen SL, Chenoweth SF, Jones M, Koh C, Sebastian A, Sigle LT, McGraw EA. 2020. Artificial selection finds new hypotheses for the mechanism of wolbachia-mediated dengue blocking in mosquitoes. *Frontiers in Microbiology* 11: 1456. DOI: https://doi.org/10.3389/fmicb.2020.01456, PMID: 32733407

Franzo G, Legnardi M, Tucciarone CM, Drigo M, Martini M, Cecchinato M. 2019. Evolution of infectious bronchiitis virus in the field after homologous vaccination introduction. *Veterinary Research* 50: 92. DOI: https://doi.org/10.1186/s13567-019-0713-4, PMID: 31706335

Gal-Mor O. 2018. Persistent Infection and Long-Term Carriage of Typhoidal and Nontyphoidal Salmonellae. *Clinical Microbiology Reviews* 32: e00088-18. DOI: https://doi.org/10.1128/CMR.00088-18, PMID: 30487167

Gandon S, Mackinnon MJ, Nee S, Read AF. 2001. Imperfect vaccines and the evolution of pathogen virulence. *Nature* 414: 751–755. DOI: https://doi.org/10.1038/414751a

Gao Y-M, Ding H, Lamberton PHL, Lu D-B. 2016. Prevalence of toxoplasma gondii in pet dogs in mainland China: A meta-analysis. *Veterinary Parasitology* 229: 126–130. DOI: https://doi.org/10.1016/j.vetpar.2016.10.009, PMID: 27809967

Gibb R, Redding DW, Chin KQ, Donnelly CA, Blackburn TM, Newbold T, Jones KE. 2020. Zoonotic host diversity increases in human-dominated ecosystems. *Nature* 584: 398–402. DOI: https://doi.org/10.1038/s41586-020-2562-8, PMID: 32759999

Gipson SAY, Hall MD. 2016. The evolution of sexual dimorphism and its potential impact on host-pathogen coevolution. *Evolution; International Journal of Organic Evolution* 70: 959–968. DOI: https://doi.org/10.1111/evo.12922, PMID: 27076194

Goic B, Stapelford KA, Frangule L, Doucet AJ, Gausson V, Blanc H, Schemmel-Jofre N, Cristofari G, Lambrechts L, Vignuzzi M, Saleh MC. 2016. Virus-derived dna drives mosquito vector tolerance to arboviral infection. *Nature Communications* 7: 12410. DOI: https://doi.org/10.1038/ncomms12410, PMID: 27580708

Gottdenker NL, Streicker DG, Faust CL, Carroll CR. 2014. Anthropogenic land use change and infectious diseases: A review of the evidence. *EcoHealth* 11: 619–632. DOI: https://doi.org/10.1007/s10393-014-0941-z, PMID: 24854248

Graham AL, Allen JE, Read AF. 2005. Evolutionary causes and consequences of immunopathology. *Annual Review of Evolution, Ecology, and Systematics* 36: 373–397. DOI: https://doi.org/10.1146/annurev.ecolsys.36.102003.152622

Graham AL. 2021. Naturalizing mouse models for immunology. *Nature Immunology* 22: 111–117. DOI: https://doi.org/10.1038/s41590-020-00857-2, PMID: 33495644

Grange ZL, Goldstein T, Johnson CK, Anthony S, Gilardi K, Daszak P, Olival KJ, O’Rourke T, Murray S, Olson SH, Ford SA, Albert I, Allen SL, Chenoweth SF, Jones M, Koh C, Sebastian A, Sigle LT, McGraw EA. 2021. Naturalizing mouse models for immunology. *PNAS* 118: e2002324118. DOI: https://doi.org/10.1073/pnas.2002324118, PMID: 33822740

Gravinattii ML, Barbosa CM, Soares RM, Gregori F. 2020. Synanthropic rodents as virus reservoirs and transmitters. *Revista Da Sociedade Brasileira de Medicina Tropical* 53: e20190486. DOI: https://doi.org/10.1590/0037-8682-0486-2019, PMID: 32049206

Gupta RK, Hué S, Schaller T, Verschoor E, Pillay D, Towers GJ. 2009. Mutation of a single residue rescues human tethersin resistant to HIV-1 vpu-mediated depletion. *PLOS Pathogens* 5: e1000443. DOI: https://doi.org/10.1371/journal.ppat.1000443, PMID: 19461879

Han BA, Kramer AM, Drake JM. 2016. Global patterns of zoonotic disease in mammals. *Trends in Parasitology* 32: 565–577. DOI: https://doi.org/10.1016/j.pt.2016.04.007, PMID: 27316904

Hansen MC, Potapov PV, Moore R, Hancher M, Turubanova SA, Tyukavina A, Thau D, Stehman SV, Goetz SJ, Loveland TR, Kommareddy A, Egorov A, Chini L, Justice CO, Townshend JRG. 2013. High-resolution global maps of 21st-century forest cover change. *Science* 342: 850–853. DOI: https://doi.org/10.1126.science.1244693, PMID: 24233722

Harrison AG, Lin T, Wang P. 2020. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. *Trends in Immunology* 41: 1100–1115. DOI: https://doi.org/10.1016/j.it.2020.05.004, PMID: 33132005

Hatziziannou T, Del Prete GQ, Keele BF, Estes JD, McNatt MW, Bitzegeio J, Raymond A, Rodriguez A, Schmidt F, Mac Trubey C, Smedley J, Piatak M, KewalRamani VN, Lifson JD, Bieniasz PD. 2014. HIV-1-induced AIDS in rodents. *Science* 344: 1401–1405. DOI: https://doi.org/10.1126/science.1250761, PMID: 24948736

Hayward AD, Nussey DH, Wilson AJ, Berenos C, Pilkington JG, Watt KA, Pemberton JM, Graham AL. 2014. Natural selection on individual variation in tolerance of gastrointestinal nematode infection. *PLOS Biology* 12: e1001917. DOI: https://doi.org/10.1371/journal.pbio.1001917, PMID: 25072883

Henschen AE, Adelman JS. 2019. What Does Tolerance Mean for Animal Disease Dynamics When Pathology Enhances Transmission? *Integrative and Comparative Biology* 59: 1220–1230. DOI: https://doi.org/10.1093/icb/icz005
Hobern D. 2021. BIOSCAN: DNA barcoding to accelerate taxonomy and biogeography for conservation and sustainability. Genome 64: 161–164. DOI: https://doi.org/10.1139/gen-2020-0009, PMID: 32268069

Holmes EC, Rambaut A, Andersen KG. 2018. Panemics: Spend on surveillance, not prediction. Nature 558: 180–182. DOI: https://doi.org/10.1038/s41586-018-05373-w, PMID: 29880819

Horns F, Hood ME. 2012. The evolution of disease resistance and tolerance in spatially structured populations. Evolution and Ecology 2: 1705–1711. DOI: https://doi.org/10.1002/ece3.290, PMID: 22957174

Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, Watts DD. 2004. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation 109: 1603–1608. DOI: https://doi.org/10.1161/01.CIR.0000124480.32233.8A, PMID: 15023877

Hu B, Huang S, Yin L. 2021. The cytokine storm and COVID-19. Journal of Medical Virology 93: 250–256. DOI: https://doi.org/10.1002/jmv.26232, PMID: 32592501

Huang ZYX, de Boer WF, van Langevelde F, Olson V, Blackburn TM, Prins HHT. 2013. Species’ life-history traits explain interspecific variation in reservoir competence: a possible mechanism underlying the dilution effect. PLOS ONE 8: e54341. DOI: https://doi.org/10.1371/journal.pone.0054341, PMID: 23365661

Huang C, Liu WJ, Xu W, Jin T, Zhao Y, Song J, Shi Y, Ji W, Jia H, Zhou Y, Wen H, Zhao H, Liu H, Li H, Wang Q, Wu Y, Wang L, Liu D, Liu G, Yu H, et al. 2016. A bat-derived putative cross-family recombinant coronavirus with a reovirus gene. PLOS Pathogens 12: e1005883. DOI: https://doi.org/10.1371/journal.ppat.1005883, PMID: 27676249

Huang YJS, Hsiai S, Vanlandingham DL. 2019. Emergence and re-emergence of mosquito-borne arboviruses. Current Opinion in Virology 34: 104–109. DOI: https://doi.org/10.1016/j.civiro.2019.01.001, PMID: 30743191

Irving AT, Ahn M, Goh G, Anderson DE, Wang LF. 2021. Lessons from the host defences of bats, a unique viral reservoir. Nature 589: 363–370. DOI: https://doi.org/10.1038/s41586-020-03128-0, PMID: 33473223

Jackson JA, Hall AJ, Friberg IM, Ralli C, Lowe A, Zawadzka M, Turner AK, Paterson S, Bradley JE, Begon M. 2014. An immunological Marker of Tolerance to Infection in Wild Rodents. PLOS Biology 12: e1001901. DOI: https://doi.org/10.1371/journal.pbio.1001901, PMID: 23004450

Jarefors S, Bennet L, You E, Forsberg P, Ekerfelt C, Berglund J, Emnerudh J. 2006. Lyme borreliosis reinfection: might it be explained by a gender difference in immune response? Immunology 118: 224–232. DOI: https://doi.org/10.1111/j.1365-2567.2006.02360.x, PMID: 16771857

Jebb D, Huang Z, Pippel M, Hughes GM, Lavrchenko K, Devanna P, Winkler S, Kermit LS, Skirmuntt EC, Katzourakis A, Burkitt-Gray L, Ray DA, Sullivan KAM, Roscito JG, Kirilenko BM, Davalos LM, Corhals AP, Power ML, Jones G, Ransome RD, et al. 2020. Six reference-quality genomes reveal evolution of bat adaptations. Nature 583: 578–584. DOI: https://doi.org/10.1038/s41586-020-2486-3, PMID: 32699395

Jiang Y, Xia T, Zhou Y, Yu L, Yang S, Huang Q, Li L, Gao F, Qu Z, Tong W, Tong G. 2015. Characterization of three porcine reproductive and respiratory syndrome viruses isolates from a single swine farm bearing strong homology to a vaccine strain. Veterinary Microbiology 179: 242–249. DOI: https://doi.org/10.1016/j.vetmic.2015.06.015, PMID: 26162970

Johnson CK, Hitchens PL, Pandit PS, Rushmore J, Evans TS, Young CCW, Doyle MM. 2020. Global shifts in mammalian population trends reveal key predictors of virus spillover risk. Proceedings of the Royal Society B 287: 20192736. DOI: https://doi.org/10.1098/rspb.2019.2736

Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P. 2008. Global trends in emerging infectious diseases. Nature 451: 990–993. DOI: https://doi.org/10.1038/nature06536, PMID: 18288193

Jeoubert PE, Wernere S, de la Calle C, Guivel-Benhassine F, Giodini A, Peduto L, Levine B, Schwartz O, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P. 2018. Pandemics: Spend on surveillance, not prediction. Nature 578–584. DOI: https://doi.org/10.1038/s41586-020-2486-3, PMID: 32699395

Jebb D, Huang Z, Pippel M, Hughes GM, Lavrchenko K, Devanna P, Winkler S, Kermit LS, Skirmuntt EC, Katzourakis A, Burkitt-Gray L, Ray DA, Sullivan KAM, Roscito JG, Kirilenko BM, Davalos LM, Corhals AP, Power ML, Jones G, Ransome RD, et al. 2020. Six reference-quality genomes reveal evolution of bat adaptations. Nature 583: 578–584. DOI: https://doi.org/10.1038/s41586-020-2486-3, PMID: 32699395

Jiang Y, Xia T, Zhou Y, Yu L, Yang S, Huang Q, Li L, Gao F, Qu Z, Tong W, Tong G. 2015. Characterization of three porcine reproductive and respiratory syndrome viruses isolates from a single swine farm bearing strong homology to a vaccine strain. Veterinary Microbiology 179: 242–249. DOI: https://doi.org/10.1016/j.vetmic.2015.06.015, PMID: 26162970

Karesh WB. 2011. Predict: Surveillance and prediction for emerging pathogens of wildlife. BMC Proceedings 5: L7. DOI: https://doi.org/10.1186/1753-6561-5-S1-L7

Kaur A, Alexander L, Staprans SI, Denekamp L, Hale CL, McClure HM, Feinberg MB, Desrosiers RC, Johnson RP. 2001. Emergence of cytotoxic T lymphocyte escape mutations in nonpathogenic simian immunodeficiency virus infection. Journal of Virology 75: 3207–3217. DOI: 10.1128/JVI.75.7.3207-3217.2001, PMID: 11745337

Kaur M, Singh K, Sidhu SK, Devi P, Kaur M, Soneja S, Singh N. 2018. Coinfection of chikungunya and dengue viruses: A serological study from North Western region of Punjab, India. Journal of Laboratory Physicians 10: 443–447. DOI: https://doi.org/10.4103/JLP.JLP_13_18, PMID: 30498319

Kemp SA, Collier DA, Datur RP, Ferreira IATM, Gayed S, Jahun A, Hosmillo M, Rees-Spear C, Mioclova P, Lumb IU, Roberts DJ, Chandra A, Temperton N, CITIID-NiHR BioResource COVID-19 Collaboration, COVID-19 Genomics UK (COG-UK) Consortium, Sharrocks K, Blane E, Modis Y, Leigh KE, Briggs JAG, et al. 2021. SARS-COV-2 evolution during treatment of chronic infection. Nature 592: 277–282. DOI: https://doi.org/10.1038/s41586-021-05373-w, PMID: 32545711

Khabbaz RF, Heneine W, George JR, Parekh B, Rowe T, Woods T, Switzer WM, McClure HM, Murphy-Corb M, Folks TM. 1994. Brief report: infection of a laboratory worker with simian immunodeficiency virus. The New England Journal of Medicine 330: 172–177. DOI: https://doi.org/10.1056/NEJM199401203300304, PMID: 8264739
Khan I, Prasad NG. 2011. Sex-specific effect of bacterial infection on components of adult fitness in *Drosophila melanogaster*. *J. Evol. Biol* Res 3: 79–86. DOI: https://doi.org/10.5897/JEBR.900014

Khan I, Agashe D, Rollf J. 2017a. Early-life inflammation, immune response and ageing. *Proceedings. Biological Sciences* 284: 20170125. DOI: https://doi.org/10.1098/rspb.2017.0125, PMID: 28275145

Khan I, Prakash A, Agashe D. 2017b. Experimental evolution of insect immune memory versus pathogen resistance. *Proceedings. Biological Sciences* 284: 20171583. DOI: https://doi.org/10.1098/rspb.2017.1583, PMID: 29237849

Klemme I, Hyvärinen P, Karvonen A. 2020. Negative associations between parasite avoidance, resistance and tolerance predict host health in salmonid fish populations. *Proceedings of the Royal Society B* 287: 20200388. DOI: https://doi.org/10.1098/rspb.2020.0388

Knutie SA, Owen JP, McNew SM, Bartlow AW, Arriero E, Thompson M, Koop JAH, Clayton DH. 2016. Galápagos mockingbirds tolerate introduced parasites that affect Darwin’s finches. *Ecology* 97: 940–950. DOI: https://doi.org/10.1890/15-0119.1, PMID: 27220210

Knutie SA, Wilkinson CL, Wu QC, Ortega CN, Rohr JR. 2017. Host resistance and tolerance of parasitic gut worms depend on resource availability. *Oecologia* 183: 1031–1040. DOI: https://doi.org/10.1007/s00442-017-3822-7, PMID: 28138818

Kohl KD, Sadowska ET, Rudolf AM, Koteja P. 2016. Experimental Evolution on a Wild Mammal Species Results in Modifications of Gut Microbial Communities. *Frontiers in Microbiology* 7: 634. DOI: https://doi.org/10.3389/fmicb.2016.00634, PMID: 27199960

Komar N, Langevin S, Hinten S, Nemeth N, Edwards E, Hettler D, Davis B, Bowen R, Bunning M. 2003. Experimental Infection of North American Birds with the New York 1999 Strain of West Nile Virus. *Emerging Infectious Diseases* 9: 311–322. DOI: https://doi.org/10.3202/eid0903.020628, PMID: 12643825

LaDeau SL, Kilpatrick AM, Marra PP. 2007. West Nile Virus emergence and large-scale declines of north american bird populations. *Nature* 447: 710–713. DOI: https://doi.org/10.1038/nature05829, PMID: 17507930

Lambrechts L, Saleh MC. 2019. Manipulating mosquito tolerance for arbovirus control. *Cell Host & Microbe* 26: 309–313. DOI: https://doi.org/10.1016/j.chom.2019.08.005, PMID: 31513769

Lefèvre T, Williams AJ, de Roode JC. 2010. Genetic variation in resistance, but not tolerance, to a protozoan parasite in the Monarch butterfly. *Proceedings of the Royal Society B* 278: 751–759. DOI: https://doi.org/10.1098/rspb.2010.1479

Lefèvre T, Vantaux A, Dabiré KR, Mouline K, Cohuet A. 2013. Non-genetic determinants of mosquito competence for malaria parasites. *PLOS Pathogens* 9: e1003365. DOI: https://doi.org/10.1371/journal.ppat.1003365, PMID: 23818841

Legrand N, Weijer K, Spits H. 2006. Experimental models to study development and function of the human immune system in vivo. *Journal of Immunology* 176: 2053–2058. DOI: https://doi.org/10.4049/jimmunol.176.4.2053, PMID: 16455958

Letko M, Seifert SN, Olival KJ, Plowright RK, Munster VJ. 2020. Bat-borne virus diversity, spillover and emergence. *Nature Reviews. Microbiology* 18: 461–471. DOI: https://doi.org/10.1038/s41579-020-0394-z, PMID: 32528128

Lewin HA, Robinson GE, Kress WJ, Baker WJ, Coddington J, Crandall KA, Durbin R, Edwards SV, Forest F, Gilbert MTP, Goldstein MM, Grigoriev IV, Hackett KJ, Haussler D, Jarvis ED, Johnson WE, Patrinos A, Richards S, Castilla-Rubio JC, van Sluys MA, et al. 2018. Earth Biogenome Project: Sequencing life for the future of life. *PNAS* 115: 4325–4333. DOI: https://doi.org/10.1073/pnas.1720115115, PMID: 29686065

Li XY, Kokko H. 2019. Intersexual resource competition and the evolution of sex-biased dispersal. *Frontiers in Ecology and Evolution* 7: 111. DOI: https://doi.org/10.3389/fevo.2019.00111

Liu P, Bai Y, Jiang X, Zhou L, Yuan S, Yao H, Yang H, Sun Z. 2018. High reversion potential of a cell-adapted vaccine candidate against highly pathogenic porcine reproductive and respiratory syndrome. *Veterinary Microbiology* 227: 133–142. DOI: https://doi.org/10.1016/j.vetmic.2018.10.004, PMID: 30473344

Mackinnon MJ, Gandon S, Read AF. 2008. Virulence evolution in response to vaccination: The case of malaria. *Vaccine* 26: C52. DOI: https://doi.org/10.1016/j.vaccine.2008.04.012

Mandl JN, Akondy R, Lawson B, Kozyr N, Staprans SI, Ahmed R, Feinberg MB. 2011. Distinctive TLR7 signaling, type I IFN production, and attenuated innate and adaptive immune responses to yellow fever virus in a primate reservoir host. *Journal of Immunology* 186: 6406–6416. DOI: https://doi.org/10.4049/jimmunol.1001191, PMID: 21515797

Mandl JN, Ahmed R, Barreiro LB, Daszak P, Epstein JH, Virgin HW, Feinberg MB. 2015. Reservoir host immune responses to emerging zoonotic viruses. *Cell* 160: 20–35. DOI: https://doi.org/10.1016/j.cell.2014.12.003, PMID: 25533784

Märkle H, John S, Cornille A, Fields PD, Tellier A. 2021. Novel genomic approaches to study antagonistic coevolution between hosts and parasites. *Molecular Ecology* 30: 3660–3676. DOI: https://doi.org/10.1111/mec.16001, PMID: 34038012

Martin DP, Biagini P, Lefèvre P, Golden M, Roumagnac P,Varsani A. 2011. Recombination in eukaryotic single stranded dna viruses. *Viruses* 3: 1699–1738. DOI: https://doi.org/10.3390/v3091699, PMID: 21994803

Martin LB, Addison B, Bean AGD, Buchanan KL, Crino OL, Eastwood JR, Flies AS, Hamede R, Hill GE, Klassen M, Koch RE, Martens JM, Napolitano C, Narayan EJ, Peacock L, Peel AJ, Peters A, Raven N, Risely A, Roast MJ, et al. 2019. Extreme competence: Keystone hosts of infections. *Trends in Ecology & Evolution* 34: 303–314. DOI: https://doi.org/10.1016/j.tree.2018.12.009, PMID: 30704782
Masri I, Schulte RD, Timmermeyer N, Thanisch S, Crummenerl LL, Jansen G, Michiels NK, Schulenburg H. 2013. Sex differences in host defence interfere with parasite-mediated selection for outcrossing during host–parasite coevolution. Ecology Letters 16: 461–468. DOI: https://doi.org/10.1111/ele.12068, PMID: 23301667

Mayer A, Mora T, Rivoire O, Walczak AM. 2016. Diversity of immune strategies explained by adaptation to pathogen statistics. PNAS 113: 8630–8635. DOI: https://doi.org/10.1073/pnas.1600663113, PMID: 27432970

Maze-Gullmo E, Loot G, Páez DJ, Lefèvre T, Blanchet S. 2014. Heritable variation in host tolerance and resistance inferred from a wild host-parasite system. Proceedings. Biological Sciences 281: 20132567. DOI: https://doi.org/10.1098/rspb.2013.2567, PMID: 24478295

McCallum M, Bassi J, De Marco A, Chen A, Walls AC, Di Iullo J, Tortorici MA, Navarro MJ, Silacci-Fregni C, Saliba C, Sprouse KR, Agostini M, Pinto D, Culap K, Bianchi S, Jaconi S, Cameroni E, Bowen JE, Tilles SW, Pizzuto MS, et al. 2021. SARS-COV-2 immune evasion by the b.1.427/b.1.429 variant of concern. Science 373: 648–654. DOI: https://doi.org/10.1126/science.abi7994, PMID: 34210893

McCarville JL, Ayres JS. 2018. Disease tolerance: Concept and mechanisms. Current Opinion in Immunology 50: 88–93. DOI: https://doi.org/10.1016/j.mco.2017.12.003, PMID: 29253642

McDonald SM, Nelson ML, Turner PE, Patton JT. 2016. Reassortment in segmented RNA viruses: Mechanisms and outcomes. Nature Reviews. Microbiology 14: 448–460. DOI: https://doi.org/10.1038/nrmicro.2016.46, PMID: 27211789

McFarlane R, Sleigh A, McMichael T. 2012. Synanthropy of wild mammals as a determinant of emerging infectious diseases in the Asian-Australasian region. EcoHealth 9: 24–35. DOI: https://doi.org/10.1007/s10393-012-0763-9, PMID: 22526750

Medzhitov R, Schneider DS, Soares MP. 2012. Disease tolerance as a defense strategy. Science 335: 936–941. DOI: https://doi.org/10.1126/science.1214935, PMID: 22363001

Meyerson NR, Sawyer SL. 2011. Two-stepping through time: Mammals and viruses. Trends in Microbiology 19: 286–294. DOI: https://doi.org/10.1016/j.tim.2011.03.006, PMID: 21531564

Miller MR, White A, Boots M. 2005. The evolution of host resistance: Tolerance and control as distinct strategies. Journal of Theoretical Biology 236: 198–207. DOI: https://doi.org/10.1016/j.jtbi.2005.03.005, PMID: 16005309

Miller MR, White A, Boots M. 2006. The evolution of parasites in response to tolerance in their hosts: The good, the bad, and apparent commensalism. Evolution; International Journal of Organic Evolution 60: 945–956. DOI: https://doi.org/10.1111/j.0014-3820.2006.tb01173.x, PMID: 16817535

Miller CVL, Cotter SC. 2018. Resistance and tolerance: The role of nutrients on pathogen dynamics and infection outcomes in an insect host. The Journal of Animal Ecology 87: 500–510. DOI: https://doi.org/10.1111/1365-2656.12763, PMID: 28975616

Mollentze N, Streicker DG. 2020. Viral zoonotic risk is homogenous among taxonomic orders of mammalian and avian reservoir hosts. PNAS 117: 9423–9430. DOI: https://doi.org/10.1073/pnas.1919176117, PMID: 32284401

Morand S, McIntyre KM, Baylis M. 2014. Domesticated animals and human infectious diseases of zoonotic origins: Domestication time matters. Infection, Genetics and Evolution 24: 76–81. DOI: https://doi.org/10.1016/j.meegde.2014.02.013, PMID: 24642136

Morse SS, Mazet JAK, Woolhouse M, Parrish CR, Carroll D, Karesh WB, Zambrana-Torrelio C, Lipkin WI, Daszak P. 2012. Prediction and prevention of the next pandemic zoonosis. Science 335: 28–36. DOI: https://doi.org/10.1186/1756-3305-6-219, PMID: 20425055

Mukherjee K, Dubovsky I, Grizanova E, Lehmann R, Vilcinskas A. 2019. Epigenetic mechanisms mediate the experimental evolution of resistance against parasitic fungi in the greater wax moth Galleria mellonella. Scientific Reports 9: 1626. DOI: https://doi.org/10.1038/s41598-018-3629-8, PMID: 30733453

Muslim A, Fong MY, Mahmud R, Lau YL, Sivanandam S. 2013. Armigeres subalbatus incriminated as a vector of zoonotic brugia Pahangi filariais in suburban Kuala Lumpur, Peninsular Malaysia. Parasites & Vectors 6: 219. DOI: https://doi.org/10.1186/1756-3305-6-219, PMID: 23898840

Nan Y, Wu C, Gu G, Sun W, Zhang YJ, Zhou EM. 2017. Improved vaccine against PRRSV: Current progress and future perspective. Frontiers in Microbiology 8: 1635. DOI: https://doi.org/10.3389/fmicb.2017.01635, PMID: 28894443

Nystrand M, Dowling DK. 2020. Effects of immune challenge on expression of life-history and immune trait expression in sexually reproducing metazoans-a meta-analysis. BMC Biology 18: 135. DOI: https://doi.org/10.1186/s12915-020-00856-7, PMID: 33028304

Obamose JO, Li H, Jia H, Han M, Zhu S, Huang C, Zhao Y, Zhao M, Bai Y, Yuan F, Zhao H, Peng X, Xu W, Tan W, Zhao Y, Yuan KY, Liu WJ, Lu L, Gao GF. 2017. The persistent prevalence and evolution of cross-family recombinant coronavirus gccdc1 among a bat population: A two-year follow-up. Science China. Life Sciences 60: 1357–1363. DOI: https://doi.org/10.1007/s11427-017-9263-6, PMID: 29299855

Oliveira JH, Bahia AC, Vale PF. 2020. How are arbovirus vectors able to tolerate infection? Dev. Comp. Immunol 103: 103514. DOI: https://doi.org/10.1016/j.devic.2019.103514

Ostfeld RS, Oliveira JH, Bahia AC, Vale PF. 2020. Life history and demographic drivers of reservoir competence for three tick-borne zoonotic pathogens. PLOS ONE 9: e107387. DOI: https://doi.org/10.1371/journal.pone.0107387, PMID: 25232722

Pandrea I, Sodora DL, Silvestri G, Apetrei C. 2008. Into the wild: Simian Immunodeficiency Virus (SIV) infection in natural hosts. Trends in Immunology 29: 419–428. DOI: https://doi.org/10.1016/j.it.2008.05.004, PMID: 18676179

Pandrea I, Apetrei C. 2010. Where the wild things are: Pathogenesis of siv infection in african nonhuman primate hosts. Current HIV/AIDS Reports 7: 28–36. DOI: https://doi.org/10.1007/s11904-009-0034-8, PMID: 20425055
Parrish CR, Holmes EC, Morens DM, Park EC, Burke DS, Calisher CH, Laughlin CA, Saif LJ, Daszak P. 2008. Cross-species virus transmission and the emergence of new epidemic diseases. *Microbiology and Molecular Biology Reviews* **72**: 457–470. DOI: https://doi.org/10.1128/MMBR.00004-08, PMID: 18772285

Patz JA, Olson SH, Ujeno CK, Gibb HK. 2008. Disease emergence from global climate and land use change. *The Medical Clinics of North America* **92**: 1473–1491. DOI: https://doi.org/10.1016/j.mcna.2008.07.007, PMID: 19061763

Pavlovich SS, Lovett SP, Koroleva G, Guitto JC, Arnold CE, Nagle ER, Kulcsar K, Lee A, Thibaud-Nissen F, Hume AJ, Mühlberger E, Uebelhoer LS, Towner JS, Rabadán-Radán, Sanchez-Lockhart M, Kepler TB, Palacios G. 2018. The egyptian Sentence reveals unexpected features of bat antiviral immunity. *Cell* **173**: 1098–1110. DOI: https://doi.org/10.1016/j.cell.2018.03.070, PMID: 29705641

Peel AJ, Baker KS, Hayman DTS, Broder CC, Cunningham AA, Fooks AR, Garnier R, Wood JLN, Restif O. 2018. Support for viral persistence in bats from age-specific serology and models of maternal immunity. *Scientific Reports* **8**: 3859. DOI: https://doi.org/10.1038/s41598-018-22236-6, PMID: 29497106

Peng C, Haller SL, Rahman MM, McFadden G, Rothenburg S. 2016. Myxoma virus m156 is a specific inhibitor of rabbit PKR but contains a loss-of-function mutation in australian virus isolates. *PNAS* **113**: 3855–3860. DOI: https://doi.org/10.1073/pnas.1515613113, PMID: 26903626

Ploegwricht RK, Eby P, Hudson PJ, Smith IL, Westcott D, Bryden WL, Middleton D, Reid PA, McFarlane RA, Martin G, Tabor GM, Skerratt LF, Anderson DL, Cramerli G, Quammen D, Jordan D, Freeman P, Wang LF, Epstein JJ, Marsh GA, et al. 2015. Ecological dynamics of emerging bat virus spillover. *Proceedings. Biological Sciences* **282**: 20142124. DOI: https://doi.org/10.1098/rspb.2014.2124, PMID: 25392474

Ploegwricht RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, Lloyd-Smith JO. 2017. Pathways to zoonotic spillover. *Nature Reviews. Microbiology* **15**: 502–510. DOI: https://doi.org/10.1038/nrmicro.2017.45, PMID: 28555073

Ploegwricht RK, Reaser JK, Locke H, Woodley SJ, Patz JA, Becker DJ, Oppier G, Hudson PJ, Tabor GM. 2021. Land use-induced spillover: A call to action to safeguard environmental, animal, and human health. *The Lancet. Planetary Health* **5**: e237–e245. DOI: https://doi.org/10.1016/S2542-5196(21)00031-0, PMID: 33684341

Plyusnin A, Morzunov SP. 2001. Virus evolution and genetic diversity of hantaviruses and their rodent hosts. *Schmaljohne CS, Nichol ST (Eds). Hantaviruses, Current Topics in Microbiology and Immunology*. Berlin, Heidelberg, Berlin: Springer. p. 47–75. DOI: https://doi.org/10.1007/978-3-642-5753-7_4

Poirier MV. 2019. A trade-off model for immunocompetence: The potential contribution of immunological regulation in invasive vertebrate success. *Journal of Experimental Zoology Part A* **331**: 478–484. DOI: https://doi.org/10.1002/jez.2314

Pontremoli C, Forni D, Cagliani R, Filippi G, De Gioia L, Povéy S, Cotter SC, Simpson SJ, Lee KP, Wilson K. 2016. Positive Selection Drives Evolution at the Host-Filovirus Interaction Surface. *Molecular Biology and Evolution* **33**: 2838–2847. DOI: https://doi.org/10.1093/molbev/msw158, PMID: 27521122

Povey S, Cotter SC, Simpson SJ, Lee KP, Wilson K. 2009. Can the protein costs of bacterial resistance be offset by altered feeding behaviour? *Journal of Animal Ecology* **78**: 437–446. DOI: https://doi.org/10.1111/j.1365-2666.2008.01499.x

Prasad NG, Hills A, Thomas-Sostman J, Sohail M, Shariq S. 2013. Support for viral persistence in bats from age-specific serology and models of maternal immunity. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **368**: 37–49. DOI: https://doi.org/10.1098/rstb.2008.0184, PMID: 18926971

Råberg L. 2014. How to live with the enemy: Understanding tolerance to parasites. *Evolutionary Biology | Immunology and Inflammation* **2**. DOI: https://doi.org/10.1007/BF02715881, PMID: 14631102

Råberg L, Graham AL, Read AF. 2009. Decomposing health: Tolerance and resistance to parasites in animals. *Oikos* **121**: 1463–1486. DOI: https://doi.org/10.1111/j.1365-2096.2008.01499.x

Rabberg L, Sand L, Read AF. 2007. Disentangling Genetic Variation for Resistance and Tolerance to Infectious Diseases in Animals. *Science* **318**: 812–814. DOI: https://doi.org/10.1126/science.1148526, PMID: 17975068

Råberg L, Graham AL, Read AF. 2009. Decomposing health: Tolerance and resistance to parasites in animals. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **364**: 37–49. DOI: https://doi.org/10.1098/rstb.2008.0184, PMID: 18926971

Råberg L. 2014. How to live with the enemy: Understanding tolerance to parasites. *PLOS Biology* **12**: e1001989. DOI: https://doi.org/10.1371/journal.pbio.1001989, PMID: 25369060

Rasche A, Souza B, Drexler JF. 2016. Bat hepadnaviruses and the origins of primate hepatitis B viruses. *Current Opinion in Virology* **16**: 86–94. DOI: https://doi.org/10.1016/j.civiro.2016.01.015, PMID: 26897577

Read AF, Baigent SJ, Powers C, Kgosana LB, Smith LP, Kennedy DA, Walkden-Brown SW, Nair VK. 2015. Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLOS Biology* **13**: e1002198. DOI: https://doi.org/10.1371/journal.pbio.1002198, PMID: 26214839

Regoes RR, McLaren PJ, Battegay M, Bernasconi E, Calmy A, Günthard HF, Hoffmann M, Rauch A, Telenti A, Fellay J, Swiss HIV Cohort Study. 2014. Disentangling human tolerance and resistance against HIV. *PLOS Biology* **12**: e1001951. DOI: https://doi.org/10.1371/journal.pbio.1001951, PMID: 25226169

Remien CH, Nuissler SL. 2020. Reservoir Population Dynamics and Pathogen Epidemiology Drive Pathogen Genetic Diversity, Spillover, and Emergence. *medRxiv*. DOI: https://doi.org/10.1101/2020.08.19.20178145

Restif O, Graham AL. 2015. Within-host dynamics of infection: From ecological insights to evolutionary predictions. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **370**: 20140304. DOI: https://doi.org/10.1098/rstb.2014.0304, PMID: 26150670

Retel C, Márkí L, Becks L, Feulner PG. 2019. Ecological and evolutionary processes shaping viral genetic diversity. *Viruses* **11**: 220. DOI: https://doi.org/10.3390/v11030220, PMID: 30841497
Robertson SJ, Hasenkugl KJ. 2006. The role of virus-induced regulatory T cells in immunopathology. Springer Seminars in Immunopathology 28: 51–62. DOI: https://doi.org/10.1007/s00281-006-0019-2, PMID: 16841143

Rohr JR, Raffel TR, Hall CA. 2010. Developmental variation in resistance and tolerance in a multi-host-parasite system: Resistance and tolerance across hosts and parasites. Functional Ecology 24: 1110–1121. DOI: https://doi.org/10.1111/j.1365-2435.2010.01709.x

Reff J, Siva-Jothy MT. 2002. Copulation corrupts immunity: A mechanism for a cost of mating in insects. PNAS 99: 9916–9918. DOI: https://doi.org/10.1073/pnas.152271999

Roy BA, Kirchner JW. 2000. Evolutionary dynamics of pathogen resistance and tolerance. Evolution; International Journal of Organic Evolution 54: 51–63. DOI: https://doi.org/10.1111/j.0014-3820.2000.tb00007.x, PMID: 10937183

Rudensky LM, Kimata JT, Benveniste RE, Overbaugh J. 1995. Progression to AIDS in macaques is associated with changes in the replication, tropism, and cytopathic properties of the simian immunodeficiency virus variant population. Virology 207: 528–542. DOI: https://doi.org/10.1006/viro.1995.1113, PMID: 7886956

Rulli MC, Santini M, Hayman DTS, D’Oдорорсо P. 2017. The nexus between forest fragmentation in Africa and Ebola virus disease outbreaks. Scientific Reports 7: 41613. DOI: https://doi.org/10.1038/srep41613, PMID: 28195145

Russell RM, Bibollet-Ruche F, Liu W, Sherrill-Mix S, Li Y, Connell J, Loy DE, Trimble M, Smith AG, Avitto AN, Gondim MVP, Plenderleith LJ, Wetzel KS, Collman RG, Ayouba A, Esteban A, Peeters M, Kohler WJ, Miller RA, François-Souquieres S, et al. 2021. C4d4 receptor diversity represents an ancient protection mechanism against primate lentiviruses. PNAS 118: e0225914118. DOI: https://doi.org/10.1073/pnas.2025914118, PMID: 33771926

Sabbatani S, Fiorino S, Manfredi R. 2010. The emerging of the fifth malaria parasite (Plasmodium knowlesi). Nature Reviews. Microbiology 8: 321–328. DOI: https://doi.org/10.1038/nri2432, PMID: 19916–9918. DOI: https://doi.org/10.1073/pnas.152271999

Schoenfeldt J, Siva-Jothy MT. 2002. The role of virus-induced regulatory T cells in immunopathology. Springer Seminars in Immunopathology 28: 51–62. DOI: https://doi.org/10.1007/s00281-006-0019-2, PMID: 16841143

Silvestri G, Sodora DL, Koup RA, Paiardini M, O’Neil SP, McClure HM, Staprans SI, Feinberg MB. 2003. Nonpathogenic SIV Infection of Sooty Mangabeys Is Characterized by Limited Bystander Immunopathology Despite Chronic High-Level Viremia. Immunity 18: 441–452. DOI: https://doi.org/10.1016/s1074-7613(03)00600-8, PMID: 12648460

Silvestri G, Paiardini M, Pandrea I, Lederman MM, Sodora DL. 2007. Understanding the benign nature of SIV infection in natural hosts. The Journal of Clinical Investigation 117: 3148–3154. DOI: https://doi.org/10.1172/JCI33034, PMID: 17975656

Silvestri G. 2009. Immunity in natural SIV infections. Journal of Internal Medicine 265: 97–109. DOI: https://doi.org/10.1111/j.1365-2966.2008.02049.x, PMID: 19093963

Simmonds P, Aiewsakun F, Katzourakis A. 2019. Prisoners of war — host adaptation and its constraints on virus evolution. Nature Reviews. Microbiology 17: 321–328. DOI: https://doi.org/10.1038/s41579-018-0120-2, PMID: 30518814
Simon-Loriere E, Holmes EC. 2011. Why do RNA viruses recombine. Nature Reviews. Microbiology 9: 617–626. DOI: https://doi.org/10.1038/nrmmicro2614, PMID: 21725337

Siva-Jothy JA, Vale PF. 2021. Dissecting genetic and sex-specific sources of host heterogeneity in pathogen shedding and spread. PLOS Pathogens 17: e1009196. DOI: https://doi.org/10.1371/journal.ppat.1009196, PMID: 33465160

Smith GD, Zani PA, French SS. 2019. Life-history differences across latitude in common side-blotched lizards (Uta stansburiana). Ecology and Evolution 9: 5743–5751. DOI: https://doi.org/10.1002/ece3.5157, PMID: 31160995

Sorè G. 2013. Immunity, resistance and tolerance in bird-parasite interactions. Parasite Immunology 35: 350–361. DOI: https://doi.org/10.1111/pim.12047, PMID: 23800152

Sparks AM, Watt K, Sinclair R, Pilkington JG, Pemberton JM, Johnston SE, McNeilly TN, Nussey DH. 2018. Natural Selection on Antihelminth Antibodies in a Wild Mammal Population. The American Naturalist 192: 745–760. DOI: https://doi.org/10.1086/700115, PMID: 30446457

Stedman KM. 2015. Deep Recombination: RNA and ssDNA Virus Genes in DNA Virus and Host Genomes. Annual Review of Virology 2: 203–217. DOI: https://doi.org/10.1146/annurev-virology-100114-055127, PMID: 26958913

Stein RA, Katz DE. 2017. Escherichia coli, cattle and the propagation of disease. FEMS Microbiology Letters 364: fnx050. DOI: https://doi.org/10.1093/femsle/fnx050, PMID: 28333229

Streicker DG, Winternitz JC, Satterfield DA, Condori-Condori RE, Broos A, Tello C, Recuenco S, Velasco-Villa A, Streicker DG, Winternitz JC, Satterfield DA, Condori-Condori RE, Broos A, Tello C, Recuenco S, Velasco-Villa A. 2017. Who acquires infection from whom and how? Disentangling multi-host and multi-mode transmission dynamics in the “elimination” era. Philosophical Transactions of the Royal Society
of London. Series B, Biological Sciences 372: 20160091. DOI: https://doi.org/10.1098/rstb.2016.0091, PMID: 28289259

Wetzel KS, Yi Y, Elliott STC, Romero D, Jacquelin B, Hahn BH, Muller-Trutwin M, Apetrei C, Pandrea I, Collman RG. 2017. CXCR6-Mediated Simian Immunodeficiency Virus SIVagmSab Entry into Sabaean African Green Monkey Lymphocytes Implicates Widespread Use of Non-CCR5 Pathways in Natural Host Infections. Journal of Virology 91: e01626-16. DOI: https://doi.org/10.1128/JVI.01626-16, PMID: 27903799

White LA, Forester JD, Craft ME. 2018. Dynamic, spatial models of parasite transmission in wildlife: their structure, applications and remaining challenges. The Journal of Animal Ecology 87: 559–580. DOI: https://doi.org/10.1111/1365-2656.12761, PMID: 28944450

White RJ, Razgour O. 2020. Emerging zoonotic diseases originating in mammals: a systematic review of effects of anthropogenic land-use change. Mammal Rev 50: 336–352. DOI: https://doi.org/10.1111/mam.12201

Wilber MQ, Carter ED, Gray MJ, Briggs CJ, Pedersen A. 2021. Putative resistance and tolerance mechanisms have little impact on disease progression for an emerging salamander pathogen. Functional Ecology 35: 847–859. DOI: https://doi.org/10.1111/1365-2435.13754

Wolfe ND, Dunavan CP, Diamond J. 2007. Origins of major human infectious diseases. Nature 447: 279–283. DOI: https://doi.org/10.1038/nature05775, PMID: 17507975

Woodall JP. 1968. The reaction of a mangabey monkey (Cercocebus galeritus agilis Milne-Edwards) to inoculation with yellow fever virus. Annals of Tropical Medicine and Parasitology 62: 522–527. PMID: 4389547

Woodford L, Rector A, Van Ranst M, Ducki A, Bennett MD, Nicholls PK, Warren KS, Swan RA, Wilcox GE, O’Hara AJ. 2007. A novel virus detected in papillomas and carcinomas of the endangered western barred bandicoot (Perameles Bougainville) exhibits genomic features of both the papillomaviridae and polyomaviridae. Journal of Virology 81: 13280–13290. DOI: https://doi.org/10.1128/JVI.01662-07, PMID: 17898069

Woolhouse MEJ, Webster JP, Domingo E, Charlesworth B, Levin BR. 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. Nature Genetics 32: 569–577. DOI: https://doi.org/10.1038/ng1202-569, PMID: 12457190

Xie X, Lewis TJ, Green N, Wang Z. 2021. Phylogenetic network analysis revealed the recombinant origin of the SARS-CoV-2 VOC202012/01 (B.1.1.7) variant first discovered in U.K. (preprint. Microbiology 1: 449840. DOI: https://doi.org/10.1101/2021.06.24.449840

Yang Z, Bielawski JP. 2000. Statistical methods for detecting molecular adaptation. Trends in Ecology & Evolution 15: 496–503. DOI: https://doi.org/10.1016/s0169-5347(00)01994-7, PMID: 1114436

Zhang ZD, Weinstock G, Gerstein M. 2008. Rapid evolution by positive darwinian selection in t-cell antigen CD4 in primates. Journal of Molecular Evolution 66: 446–456. DOI: https://doi.org/10.1007/s00239-008-9097-1, PMID: 18414925

Zhang G, Cowled C, Shi Z, Huang Z, Bishop-Lilly KA, Fang X, Wynne JW, Xiong Z, Baker ML, Zhao W, Tachedjian M, Zhu Y, Zhou P, Jiang X, Ng J, Yang L, Wu L, Xiao J, Feng Y, Chen Y, et al. 2013. Comparative analysis of bat genomes provides insight into the evolution of flight and immunity. Science 339: 456–460. DOI: https://doi.org/10.1126/science.1230835, PMID: 23258410

Zhou L, Ge X, Yang H. 2021. Porcine Reproductive and Respiratory Syndrome Modified Live Virus Vaccine: A “Leaky” Vaccine with Debatable Efficacy and Safety. Vaccines 9: 362. DOI: https://doi.org/10.3390/vaccines9040362, PMID: 33918580

Zuk M, Stoehr AM. 2002. Immune defense and host life history. The American Naturalist 160: S9–S22. DOI: https://doi.org/10.1086/342131, PMID: 18707455