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

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Abstract

Researchers worldwide are repeatedly warning us against future zoonotic diseases resulting from mankind's insurgence into natural ecosystems. The same zoonotic pathogens that cause severe infections in a human host 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 analyse 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 harbouring rare alive-on-arrival variants with extended infectivity to new hosts (i.e., spillover). Finally, we end by underscoring the indispensability of a large multi-disciplinary empirical framework to explore the proposed link between evolved tolerance, pathogen prevalence and spillover in the wild.

Introduction

Frequent emergence of infectious zoonotic 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 and disease dynamics can shed light on potential future transmission events. Tracking ecological conditions underlying spillover events, where zoonotic pathogens overcome the species barrier 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 harbour 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 harbour a diverse array of pathogens capable of causing severe diseases in humans (Han et al., 2016)— including pathogens that can directly cause disease in humans (*Plasmodium knowlesi*) or after a host-switch (e.g., SIV) (Sabbatani et al., 2010; Sharp and Hahn, 2011). 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 rats) and domestic (e.g., dogs) species that are known to share more zoonotic pathogens with humans than other animal taxa (Gibb et al., 2020; McFarlane et al., 2012). However, in these examples, regardless of whether spill overs are mediated via phylogenetic relatedness or spatial proximity, the most fundamental criterion remains the maintenance of a stable and diverse zoonotic pool in the reservoir species. Indeed, this is supported by recent evidence suggesting that the risk of specific groups of emerging viruses that infect humans increases proportionally with a diverse “zoonotic pool” of viruses maintained by reservoir animals (Mollentze and Streicker, 2020).

How do reservoir species manage to support the circulation of zoonotic pathogens capable of infecting other susceptible hosts? The answer lies in specific ecological, life-history and physiological features of reservoir hosts that allow both 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 seven 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 which 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 two months (Capparelli et al, 2009). In fact, 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 animals from eliminating these pathogens via an effective immune response? Although the mechanisms are not always clear (Gal-Mor, 2018), these examples perhaps hint at the unique adaption of the immune system in reservoirs. Understanding the

ecological contexts and evolution of such interactions between the immune system and pathogens is necessary not only to explain the persistence of zoonotic pathogens but perhaps 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 reservoir harbouring 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., 2020; Pandrea and Apetrei, 2010). Bats and rodents, which harbour more than 60% of known zoonotic pathogens, are classical examples of such reservoir hosts (Jones et al., 2008), as they are capable of asymptomatically 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 often mediated via their over-reactivity (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 - present) which has already caused more than 2.6 million deaths within 1.5 years (https://covid19.who.int/). Although the mechanism through which SARS-CoV-2 induces mortality remains a mystery, increased morbidity of humans are indeed associated with a 'cytokine storm' produced by over-reactive TNF (Tumour necrosis factor)-α and IFN-ɣ, triggering severe damages including multi-organ failure and sepsis (Ayres, 2020; Azkur et al., 2020). 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 defence 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, 2007; Schneider and Ayres, 2008), which is perhaps a more meaningful strategy from 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, with strong implications for emerging diseases (Mandl et al., 2015; Oliveira et al., 2020). However, despite this clear conceptual link, there is a lack of enough effort to reveal and test these

connections in the natural host-pathogen systems (but see Guito et al. 2020). How are emerging infections modulated by the complex interplay between the host immune strategies and pathogen populations at an ecological scale? While studies of several emerging viral diseases in human cell lines and other laboratory models have been highly successful in shedding light on proximate host defence mechanisms and strategies used by viruses to counteract them (Legrand et al., 2006), 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 2020).

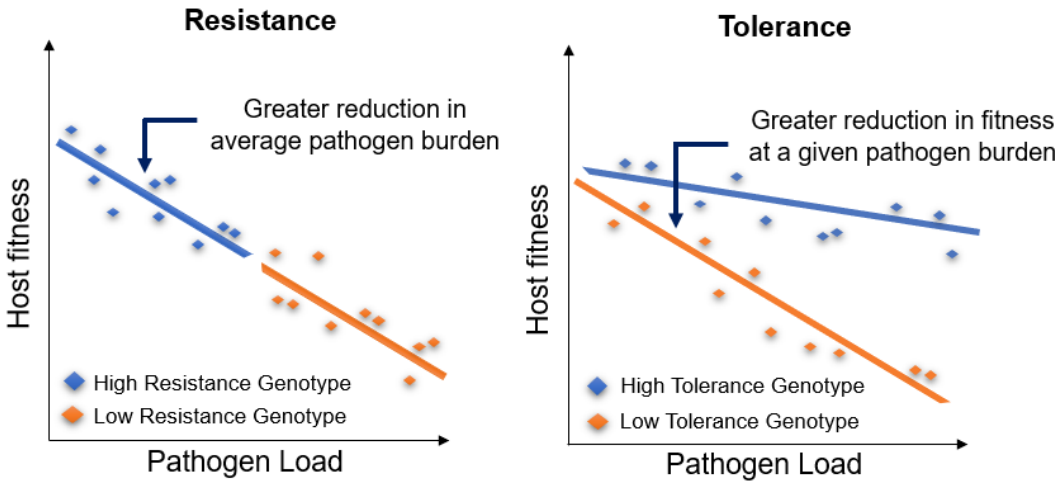

Figure 1: Outlining the conceptual difference between resistance vs tolerance: Defence mechanisms against invading pathogens can either include eliciting immune responses to detect and eliminate pathogens (Resistance) or mitigate the fitness costs of infection or immune activation without directly reducing the pathogen load (Tolerance). Different genotypes are initially exposed to the same number of pathogens. Figure plotted based on hypothetical data and adapted from Råberg et al., 2007.

In this review, we have primarily addressed how disease tolerance in reservoir species can be intrinsically linked to the maintenance and transmission risk of pathogens and successful spillover to novel hosts. We have first discussed why and how tolerance might naturally evolve during long-term association between natural hosts and pathogens as an effective strategy, followed by outlining the favourable ecological and evolutionary contexts *vis-à-vis* host-pathogen interactions where the spillover risk is likely to increase (See **Figure 2 for a brief conceptual outline**). Finally, we have ended by highlighting the importance of a systematic empirical framework to test various hypotheses on disease tolerance and its plausible evolutionary ecological role in spillover and emerging infections. With growing evidence of disease tolerance in natural host-pathogen systems, we hope that a detailed understanding of its evolutionary causes and consequences might provide new impetus to infectious disease research and pandemic preparedness.

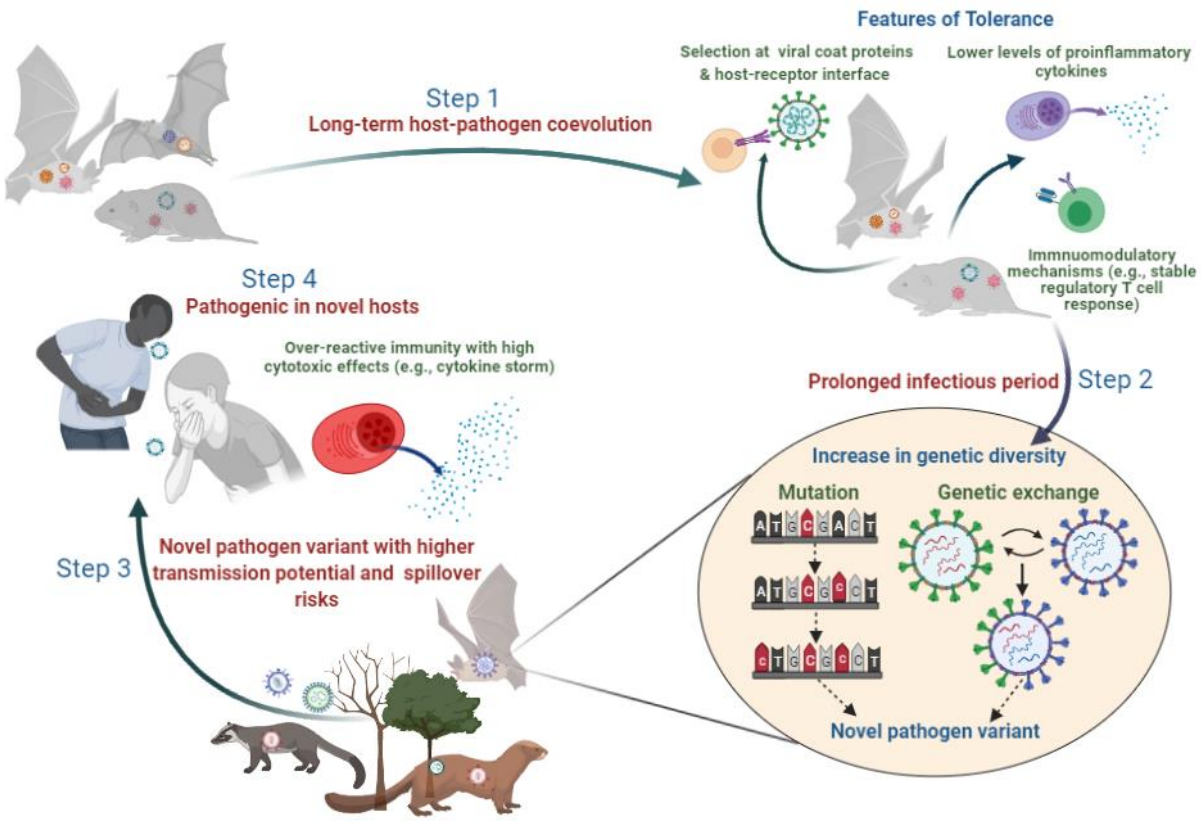

Figure 2: **Plausible sequence of events leading to the emergence of zoonotic diseases from tolerant reservoir hosts**.

- Step 1: Long-term coevolution with natural pathogens might lead to specific adaptation of the immune system of reservoir species such that they can tolerate pathogens by reducing their counteractive inflammatory responses or evolving various immunomodulatory responses (e.g., altered activity of regulatory T-cells) (Pavlovich et al, 2018; Robertson and Hasenkrug 2006).
- Step 2: Tolerant hosts with reduced inflammatory responses can support the circulation of diverse pathogen species and strains. A longer infectious period within tolerant hosts also provides an accurate ecological niche where pathogens can acquire newer mutations over time or undergo genetic exchanges and re-assortments to produce novel variants (Domingo-Calap, 2019; Jones et al, 2021).
- Step 3: Although the risk of infecting a completely new host might be rare, some of these pathogen variants with altered genetic construct might be able to cross the species barrier and infect a new host more effectively (Mandl et al, 2015).
- Step 4: When novel hosts (e.g., humans or domestic animals) come into contact with these pathogens, they might face severe illness as they are unable to tolerate the impacts of infection or lack mechanisms to reduce the cytotoxic effects of inflammatory responses (e.g., cytokine storm during SARS-CoV2) (Azkur et al, 2020).

Relevance of evolving tolerance in natural host-pathogen systems

Immune strategies are not only contingent on how hosts and pathogens interact, but also depends 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 (i.e., immunopathology; Khan et al., 2017a; Schneider and Ayres, 2008)— e.g., depending on what types of cells and organs are getting damaged, immunopathology can ultimately lead to disruption of normal physiology and impose life-long pathological consequences (Auten and Davis, 2009). Do high costs of such inflammatory responses against pathogens tilt the balance in favour 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.

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 harbour high viral titres without showing any significant morbidity, suggesting features of infection tolerance (Komar et al., 2003; LaDeau et al., 2007). Hawai'i 'Amakihis (*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 harbouring 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*) showed 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 over-induction of inflammatory pathways. 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 are known to initiate an antiviral immune cascade with reduced inflammatory capacity, they also seem to use natural killer (NK) cell receptors with distinct inhibitory signalling

components, allowing them to asymptomatically harbour 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 enabled these bats to tolerate multifarious viral infections (Ahn et al., 2019), effectively avoiding immunopathological damages caused by cytotoxic intermediates of immune pathways (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 minimise DNA damage caused by free radicals generated during their increased metabolic activity while flying (Irving et al., 2021; Zhang et al., 2013), highlighting the liaison between immunity and key host life-history adaptations. The Sooty mangabeys (*Cercocebus atys*), infected with simian immunodeficiency virus (SIV), also display limited immune activation and fail to mount active pro-inflammatory cellular immune responses (Silvestri et al., 2003). Besides, they are also able to maintain normal rates of peripheral mature $CD4^+$ 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 to allow viral persistence (Robertson and Hasenkrug, 2006). 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 upregulates cytokines that correspond to Treg responses, prolonging the viral presence (Ermonval et al., 2016). Norway rats (*Rattus 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 and FoxP3 to prevent inflammation-related pathology at sites of increased SEOV replication (Easterbrook and Klein, 2008). Taken together, it appears that several reservoir hosts have repeatedly evolved multifarious compensatory mechanisms to maintain a balanced immune system to tolerate circulating pathogens and mitigate the negative effects of over-activated inflammatory responses.

A growing body of evidence for pathogen tolerance is also coming from arthropod vectors where they evolved mechanisms to efficiently repair the damages caused by pathogens, allowing them to have both normal lifespan and persistent infection. For example, while dengue virus infection in *Aedes aegypti* causes apoptosis in the midgut, mosquito hosts, in turn, improve the maintenance of midgut homeostasis and tissue integrity via careful regulation of interstitial stem cell (ISC) proliferation which helps them to tolerate the effects of viral infection (Oliveira et al., 2020). Also, expression of neural factor (AaHig) in *A. aegypti* restrict the neuronal apoptosis caused by flavivirus infection, by preventing internalization in the mosquito cells and their amplification in the brain (Xiao et al., 2015). Consequently, unlike humans, flavivirus infection in a mosquito's nervous system does not lead to severe pathological consequences (Dharmarajan et al., 2019; Hill et al., 2014; Seifert et al., 2013). Together, these studies thus reemphasise that both disease reservoirs and vectors have evolved in various ways to subvert the negative impacts of persistent infections. Yet, a major gap in our understanding is that none of these previous experiments could reveal how these features arose in these hosts.

So, what drives the evolution of tolerance?

Although experimental results are limiting, one of the most compelling results in recent years was provided by Hayward and co-workers where they not only showed tolerance in wild sheep (*Ovis aries*) 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 body weight more slowly with increasing pathogen burden (i.e., more tolerant, Fig 1) had higher lifetime reproductive success, indicating 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 actually evolved under a strong directional selection. These results conform with existing theoretical models which 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 non-tolerant 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 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 trait 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., 2011).

The role of a long-term coevolutionary history of natural reservoirs and their pathogens is perhaps unequivocal while analysing the evolutionary basis of tolerance. However, in most cases, it is quite difficult to validate the causal link between coevolutionary history and micro-evolutionary processes leading to the evolution of tolerance in natural hosts, producing non-severe infection outcomes, 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 more tolerant Alabama population expressed lower levels of pro-inflammatory cytokine (IL-1β) and higher levels of anti-inflammatory cytokine (IL-10), hinting at the prospective link between lower inflammatory signalling and higher tolerance ability (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 characteristics of higher tolerance, compared to populations with little exposure to the parasite (Dharmarajan et al., 2019), with major consequences for vector-borne disease dynamics. 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 co-evolutionary history with lentiviruses, dating back to 5-6 million years (Compton and Emerman, 2013), countering the deleterious consequences of SIV infections (Rudensey et al, 1995). Taken together, while these examples might 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 exposed to a novel pathogen that they have not coevolved with.

In recent decades, the altered trajectory of host-pathogen interactions and coevolutionary dynamics possibly also have more obvious implications for disease spread from animals to humans, associated with rapid deforestation and land-use changes (Bloomfield, 2020; Plowright et al., 2021). For example, landscapes with patches of forests, are likely to have increased spatial overlap between wildlife, livestock and humans, presenting ideal ecological conditions for transmission of zoonotic pathogens residing in naturally tolerant wildlife hosts and 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 while engaged in mining due to infection caused by fungus *Histoplasma*, rarely found in China but prevalent in America, mostly isolated from soil samples containing decaying bat and bird faeces (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 this 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 be released by its reservoir hosts either directly into the environment or a new host through consumption, animal bites or sexual interactions (Webster et al., 2017), initiating the spillover. Also, pathogens should 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 will dictate the success of the consecutive step (Wolfe et al., 2007). However, before all these fine-scale micro-evolutionary downstream processes can begin, one of the most critical steps is to maintain a sufficiently large and diverse zoonotic pathogen pool with the potential to overcome the species barrier. Incidentally, while the role of reduced inflammation and disease tolerance in maintaining persistent zoonotic pathogen populations in reservoir species has already been implicated (Pavlovich et al., 2018; Martin et al., 2019), how it can boost the transmission potential and spillover risk is relatively unclear.

Tolerance might increase infectious period, pathogen genetic diversity and transmission

Perhaps, physiological mechanisms underlying the tolerance response play important roles (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 efficient repair mechanism to counter the damages caused by the pathogen and immune responses (Henschen and Adelman, 2019). Host can generate new cells to replace injured tissues (Medzhitov et al., 2012), as observed in the case of micro-haemorrhages 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 and 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 prolonged pathogen shedding, ramping up the risk of contacts among infected and susceptible hosts (Adelman and Hawley, 2017; VanderWaal and Ezenwa, 2016). This is consistent with a previous theoretical model which suggested that tolerance can increase the overall disease burden in host populations, by transmitting the infection to other non-tolerant susceptible individuals sharing the same ecological niche (Horns and Hoods 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 minimised, suggesting a joint role of demography and tolerance on disease spread. A recent study on African straw coloured fruit bats (*Eidolon helvum*) strongly support this possibility where small isolated populations were indeed found to be associated with high 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.

Additionally, 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. Instead, the emergence of novel zoonotic pathogens also depends on the diversity of the pathogen pool (Wolfe et al., 2007), allowing the circulation of specific rare variants which are inherently more competent to establish infection in the novel host (Mandl et al., 2015). Increased strain diversity might be particularly useful here to improve the pathogen's prospect of jumping across species barrier by harbouring the pool of useful mutations to establish infection in a new host. For instance, 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 their ability to detect antigens and initiate counter-effective immune responses (Burmeister et al., 2016; Retel et al., 2019). Such alterations are perhaps also useful to evade immune responses and establish infection in a new host.

In fact, an interesting situation might also arise when hosts harbour 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 (Bono et al., 2013). While this provides a clear example where the ability to infect new hosts arose as a function of competitive interactions, it can in principle have strong implications for disease transmission and spillover as well, provided the probability of such interactions intensifies inside a tolerant host. 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 genomic segments (McDonald et al., 2016). Here, revealing the mechanisms, such as the presence of co-infecting strains (Tao et al., 2015) and longer incubation period, that increase the chances of re-assortment might be crucial to calculate the probability of how novel genome combinations can arise to create pathogens with emergent properties— a key step in the emergence of some new influenza subtypes with expanded host range and novel antigenic properties (Jones et al. 2021).

Another related situation might arise when host immunity senses different pathogens with substantial overlap between their genomic composition or virulence genes (i.e., virotypes) (Iwasaki, 2012). For example, both Yellow Fever Virus (YFV) and SIV stimulate type I IFN upon recognition by TLR7 (Mandl et al., 2011) in their natural host Sooty Mangabeys (Woodall, 1968). Since the host shows tolerance to both the viruses and remains disease-free (Mandl et al., 2015), they can create a unique niche to stay inside the hosts for long, interchanging genomic sequences and undergo recombination to create new viral strains. Although not tested empirically, additional support for the possibility of genetic exchanges between cohabiting pathogens might come from a recently identified novel coronavirus (labelled as Ro-BatCoV GCCDC1) found in *R. leschenaultia*, which carried a functional p10 gene, required for the formation of cell syncytia, most likely derived from another 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 completely novel viruses with emergent transmission potential (Huang et al., 2016). Another example is the novel bandicoot papillomatosis 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 (Woolford et al., 2007). Such instances (and perhaps many more that awaits discovery in future) indicate that genetic exchange between diverse groups of pathogens is indeed possible in natural conditions. While exact ecological conditions where genetic exchanges between different pathogens and their evolution took place is often difficult to trace, but as described earlier, the possibility of these changes can increase proportionally with the time spend together inside a tolerant host. For example, longitudinal observation of one population of *R. leschenaultii* bats for two years found recombinants of RdRp (RNA dependent RNA polymerase) and p10 genes in Ro-BatCoV GCCDC1 within as early as five months since the initial surveillance began (Obameso et al., 2017).

Supporting evidence 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, rather than preventing the infection, pathogen replication and transmission (i.e., leaky vaccines) (Kupferschmidt, 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 non-vaccinated hosts (compare with Horns and Hoods 2012 model). For example, most 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 novel viral strains to emerge, persist, circulate and transmit effectively which otherwise would have been lethal for the chicken host to carry. Future studies should certainly investigate the causal role of tolerance in these different contexts to verify whether it actually creates the likely niche for pathogens to remain inside the hosts and facilitate genetic mechanisms to create new emerging variants— some of which might just be competent enough to cause spillover by infecting new hosts more successfully.

An integrated immune-centric experimental paradigm

Host immune strategies, ecology and pathogen prevalence all play instrumental roles in facilitating spill over, 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 sub-optimal levels in the wild due to constraints from available resources and physiological state (Viney and Riley, 2017), with strong implications for pathogen tolerance and increased prevalence. 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 effects of 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 program, aiding biological risk assessment of future EIDs (See **Figure 3** for a brief outline of the experimental paradigm).

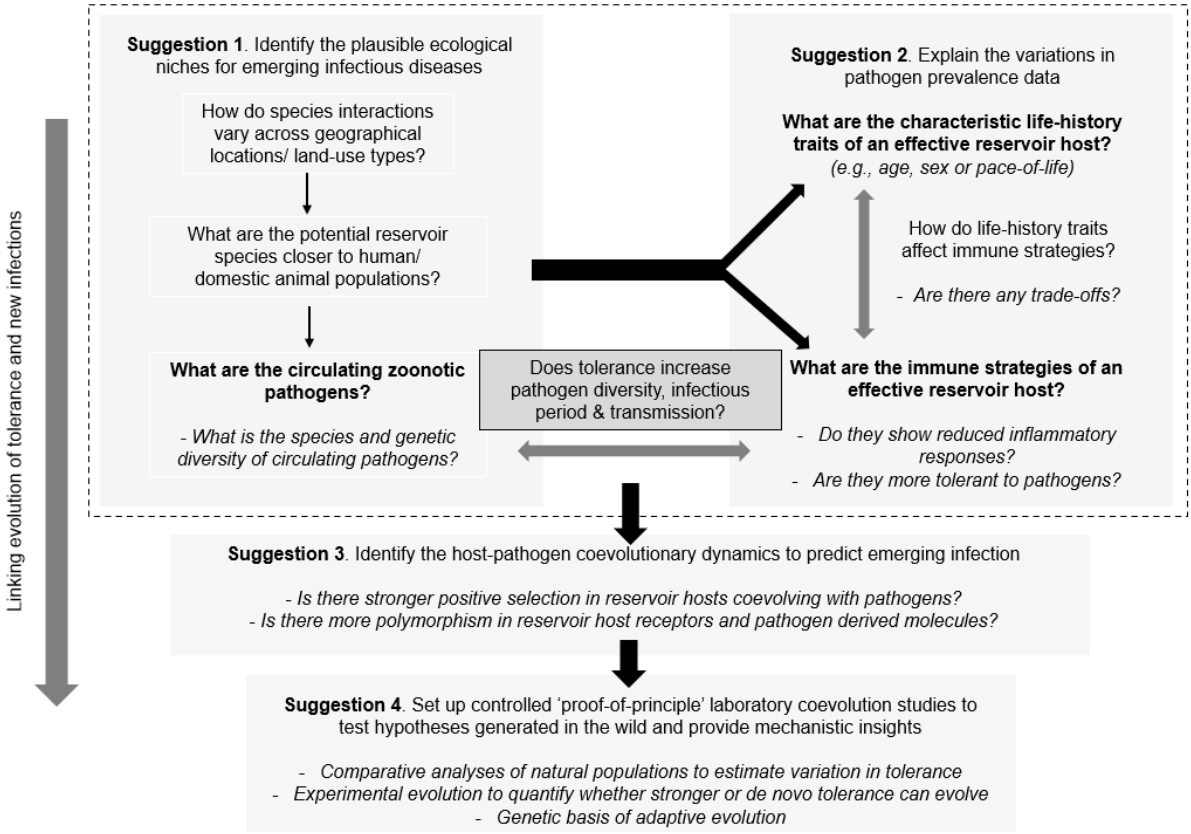

Figure 3. Outline of the proposed experimental paradigm, linking host ecology, tolerance and immune responses, and life-history to understand the natural contexts of emerging infections. While performing the traditional disease surveillance program, information on ecology, life-history, and immune strategies of potential reservoirs can be gathered in parallel to explain why and how zoonotic pathogens are distributed in the wild (Suggestion 1 and 2). Once potential reservoir hosts and zoonotic pathogens are identified, their associations can be tested for signatures of coevolution and compared with overlapping populations of novel hosts (e.g., humans or domestic animals) to analyse the observed polymorphism of molecules involved in reservoir host-zoonotic pathogen interactions, divergence in infection outcomes and immune strategies (Suggestion 3). Finally, controlled laboratory experiments can be performed to test causal links between host-pathogen coevolution, pathogen tolerance and prevalence (Suggestion 4).

<u>Suggestion 1. Identify the plausible ecological niches for emerging infectious diseases</u>

Our understanding of emerging diseases from natural reservoirs have 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 harbour 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, 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 of 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 and Wildlife Disease Surveillance Focus Group, 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 provide unique ecological niche catering to diverse host-pathogen interactions. More information across different locations can 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 (Patz et al., 2008; Daszak, 2000; Gibb et al., 2020). Some of the ecological mechanisms predicted to influence the disease transmission dynamics in anthropogenically modified habitats are certainly the changes in the niche of the interacting species (host/vector/pathogen), their altered behaviour, distribution in space and animal movement patterns (Gottdenker et al., 2014). 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 emerging infectious diseases (Coker et al., 2011). We strongly recommend a long-term disease surveillance program where multiple such regions should be first identified to understand whether and how altered species interactions are responsible for pathogen abundance and occurrence in different animal hosts, followed by tracking how it eventually influences the pathogen communities (with zoonotic potential) found in overlapping human populations.

Suggestion 2. Explain the observed variations in pathogen prevalence data

An integrated program to catalogue pathogens across species, populations and locations, as described above, will prepare a unique stage to subsequently ask more mechanistic questions to explain 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 importance. Tracing the link between variations in inflammatory responses, pathogen abundance and diversity, and the ability to tolerate infections can provide insightful evidence about how the infection outcomes and their downstream effects on pathogen transmission by potential reservoirs vary across populations. However, estimating zoonotic pathogen load in wild reservoirs and linking them to changes in their fitness proxies (i.e., 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. We explicitly propose the need to design long-term studies to first understand the basic life-history of reservoir species in the wild to standardise fitness measurements and their response to pathogens of significant zoonotic interests (e.g., counting number of circulating haemocytes, antibody titres), allowing the understanding of the actual ecological role of zoonotic infections and disease manifestation in host populations. 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. In fact, rodents can be used as model species as they are one of the largest disease reservoirs (Gravinatti et al., 2020), ubiquitously found in all ecosystem; and the immune system of several highly abundant rodent species such as *Rattus rattus* or *Mus musculus* are well-characterized (Abolins et al., 2017; Viney et al., 2015). Future studies can design assays for fitness proxies and disease tolerance in various ecosystems based on previous rodent experiments, where both cross-sectional destructive sampling to obtain precise measurements as well as 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 host 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 reservoirs species in the ecological community can overcome these limitations, enabling 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., 2020).

Developing standardized sets of reagents for rapid serological assays of immunoglobulins and key cell types such as resident memory T cells which 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.

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 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 can afford to maintain pathogens by altering their so-called combative and counteractive immune strategies (Valenzuela-Sánchez et al., 2021) (See **Figure 4** for a few general predictions linking immunity and life-history).

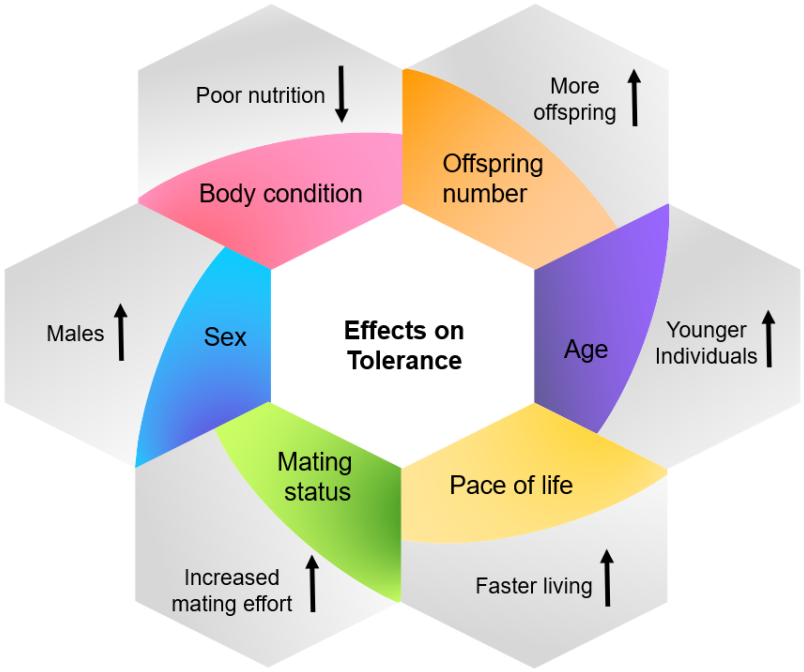

Figure 4: Outlining how different life-history traits such as age (Medzhitov et al., 2012), sex (Streciker et al., 2016), reproduction (Ostfeld et al., 2014), mating activities (Han et al., 2016), body condition (Knutie et al., 2017) and pace-of-life (Gibb et al., 2020) might contribute to the variation in tolerance levels of natural reservoirs. ‘ ’ denotes increase in tolerance while ‘ ’ denotes decrease in tolerance levels.

Males are more likely to harbour 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 which 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 favour pathogen tolerance. For example, several host species like rodents which thrive in human-dominated landscapes usually have a fast pace of life, reducing investment in immunity and thereby, harbouring more pathogens at any given time-point (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). Stressful environments such as poor nutrition or lack of nutritional supplements can also have severe impacts on immune investment and pathogen tolerance (Wang et al., 2016). Indeed, burying beetle (*Nicrophorus vespilloides*) feeding on 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 divergent impacts of nutrition. Nonetheless, considering these multifaceted implications of host physiology and various life-history traits in immunity and disease tolerance, it is imperative to jointly consider these parameters to analyse the pathogen prevalence data collected during disease surveillance.

Suggestion 3. Identify the host-pathogen coevolutionary dynamics to predict emerging infections

Analysing 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; ACE2) have been shown to undergone positive selection across different mammalian orders (Pontremoli et al., 2016; Wang et al., 2020). Quantifying selection pressures acting at various host receptor-pathogen interfaces by calculating respective dN/dS ratios (Yang and Bielawski, 2000) can help us in unearthing evidence of the evolutionary history of exposure (e.g., High or low degree of filovirus exposure to natural reservoir bat vs. novel human hosts respectively). The consequences of long-term positive selection on pathogens might transcend into evolved variants with new antigenic property and possible expansion of host range (Bedi et al., 2013). Indeed, in case of SARS outbreak in 2002, positive selection on the spike gene of SARS-CoV was positively correlated with its spillover from palm civets to

humans (The 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 (The Chinese SARS Molecular Epidemiology Consortium, 2004).

Levels of pathogen sequence divergence can further accelerate 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 analysed 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 SARSr-CoV, coronavirus isolated from the same species of bats (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. 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. In addition to finding associations between host immunity, tolerance and life-history, and pathogen prevalence, revealing coevolutionary dynamics and resulting genetic diversification of circulating pathogens can greatly advance our understanding of the natural stage for 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 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 model and track host-pathogen dynamics and test the evolution of host tolerance, genetic diversifications of pathogens and spillover risk to overlapping susceptible host populations. Due to rapid generation time and easy maintenance, insect hosts, in particular, provide an excellent system to conduct such long-term evolution experiments with pathogens (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 which exert strong selection pressure in mosquito hosts by inducing high mortality can be a valuable resource to test whether fitness costs are minimised by evolving tolerance (Aliota et al., 2010; Bartholomay, 2014). Experimental evolution studies can be combined with comparative data where multiple wild-caught mosquito populations can be first analysed to quantify the natural variation in tolerance to filarial worms and to probe 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 to establish the causal links with coevolutionary history (See **Figure 5**).

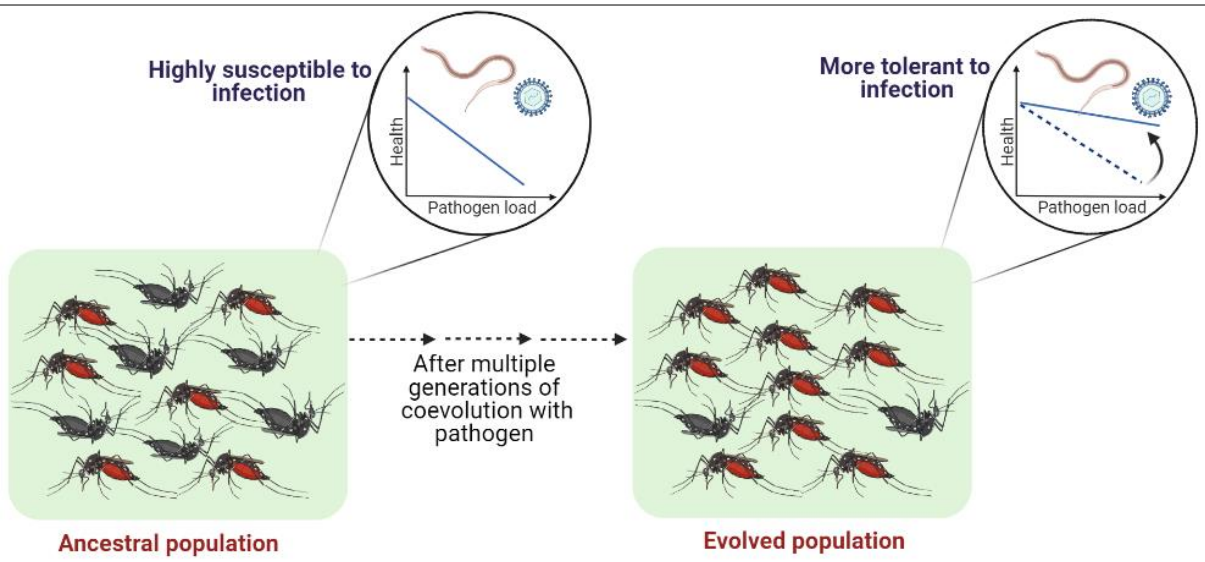

Figure 5: Outlining the controlled laboratory experimental evolution framework to test the link between coevolutionary history and tolerance. Susceptible host populations can be exposed to the coevolving pathogens at every generation and assayed periodically to estimate the changes in the tolerance level.

A similar experimental paradigm can also be used to test whether shared evolutionary history is indeed 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, 2007) which is perhaps not as prevalent as *B. pahangi* in the mosquito hosts (Muslim et al., 2013). In fact, mosquito hosts resist *Brugia malayi* infection using costly immune responses (Aliota et al., 2010,

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, followed by revealing the genetic basis of evolved immune responses (e.g. possible modulation of costly inflammatory responses) and changes in pathogen replication and transmission potential (Siva-Jothy and Vale, 2021).

Laboratory evolution studies can also be implemented to track the evolutionary origin of known mechanisms underlying tolerance strategies adopted by vector hosts. For example, both *Aedes albopictus* and *Aedes aegypti* can rapidly synthesise 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 (a) collect naturally-isolated *Aedes* populations lacking (or with inherently lower) viral tolerance; (b) impose long-term viral selection to directly test whether stronger tolerance is correlated with increased vDNA synthesis and (c) finally, test whether such evolved tolerance can be reversed by reducing vDNA synthesis to verify the 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), direct experiments showing the evolution of parasite tolerance and infectivity in important vectors is timely and will have crucial implications for 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 that increase spillover risk is far from complete and 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 over-simplistic assumptions might have limited inferential value in nature. In this review, we have highlighted the need for 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. We have proposed the identification of links between pathogen prevalence, pathogen diversity and host tolerance across a range of ecological contexts. 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 understanding. 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 non-infectious diseases (e.g., increased risk autoimmune disorders in geographical regions where improved hygiene has reduced pathogen burden) (Bach, 2018).

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Author Contributions

IK and SS developed the idea; SS and IK wrote the manuscript; GD contributed to developing several sections and edited the manuscript

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Competing interests

We have no competing interests

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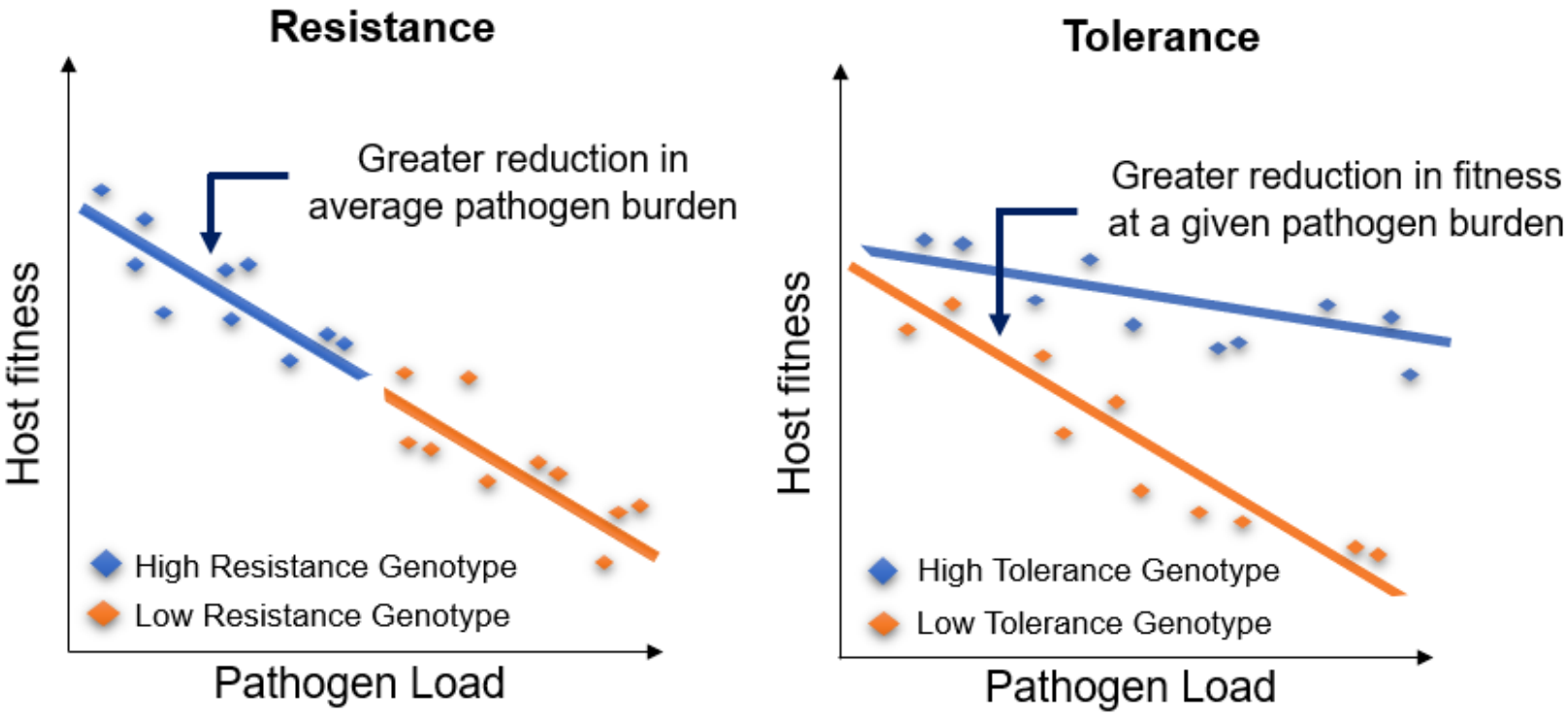
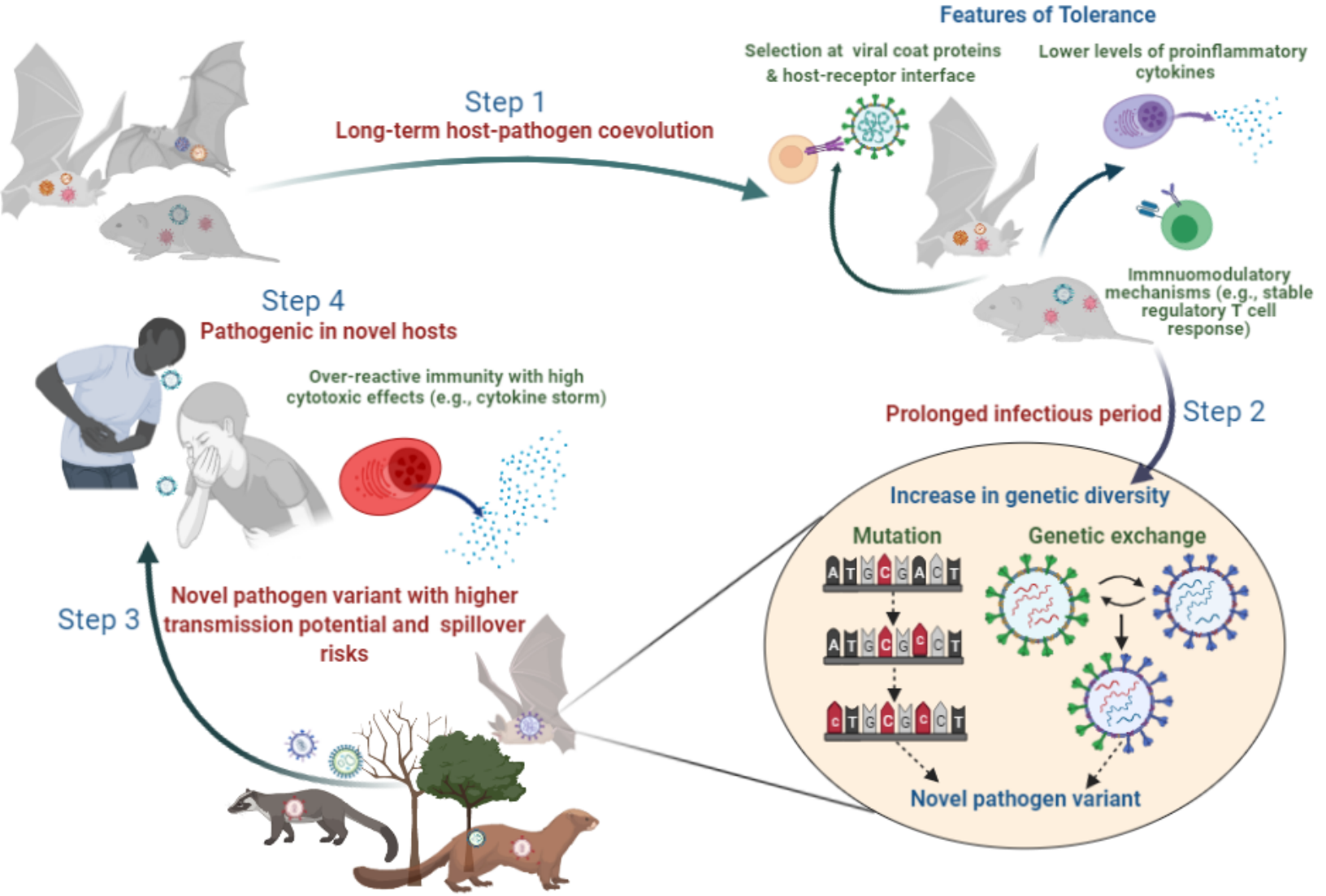
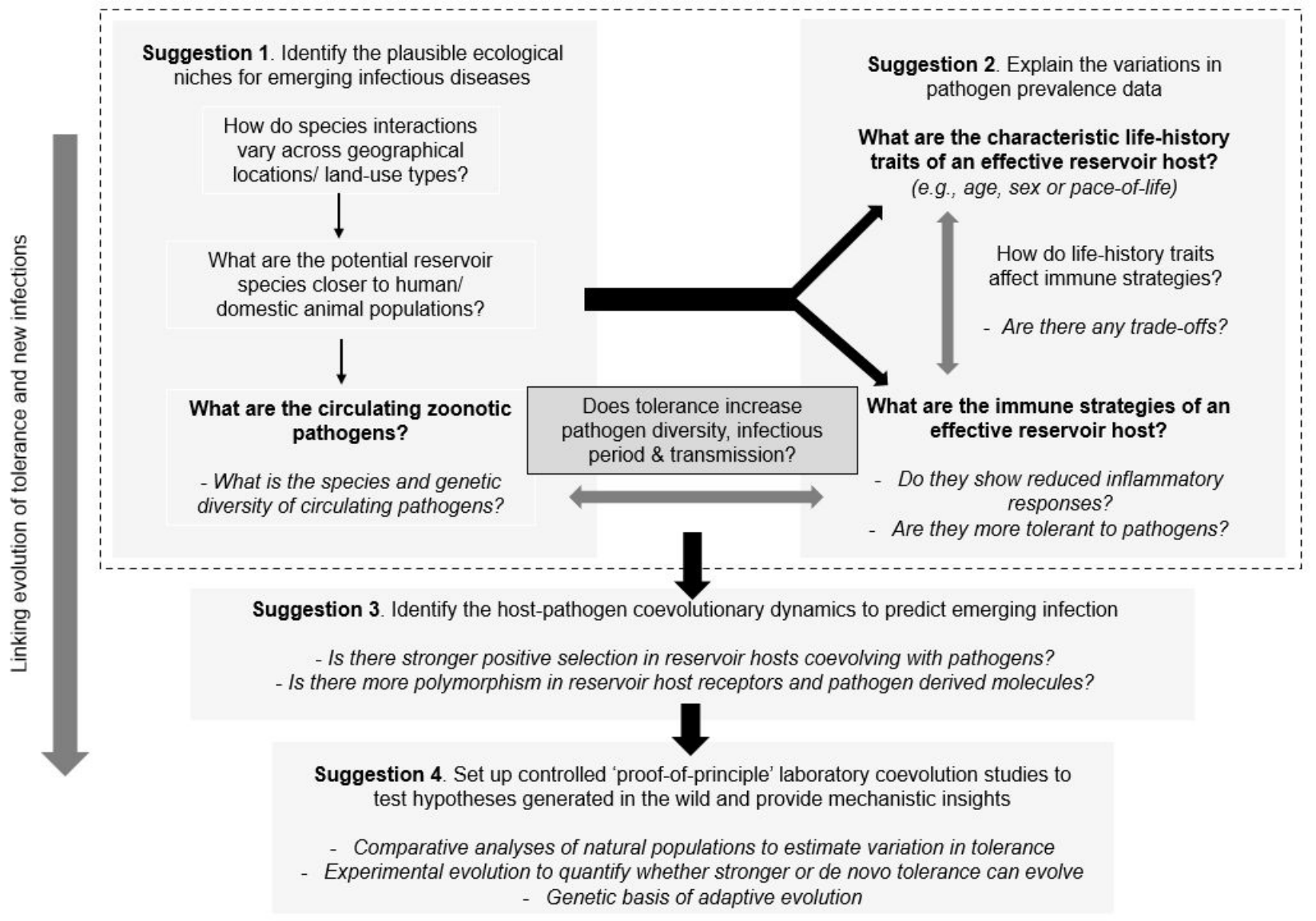
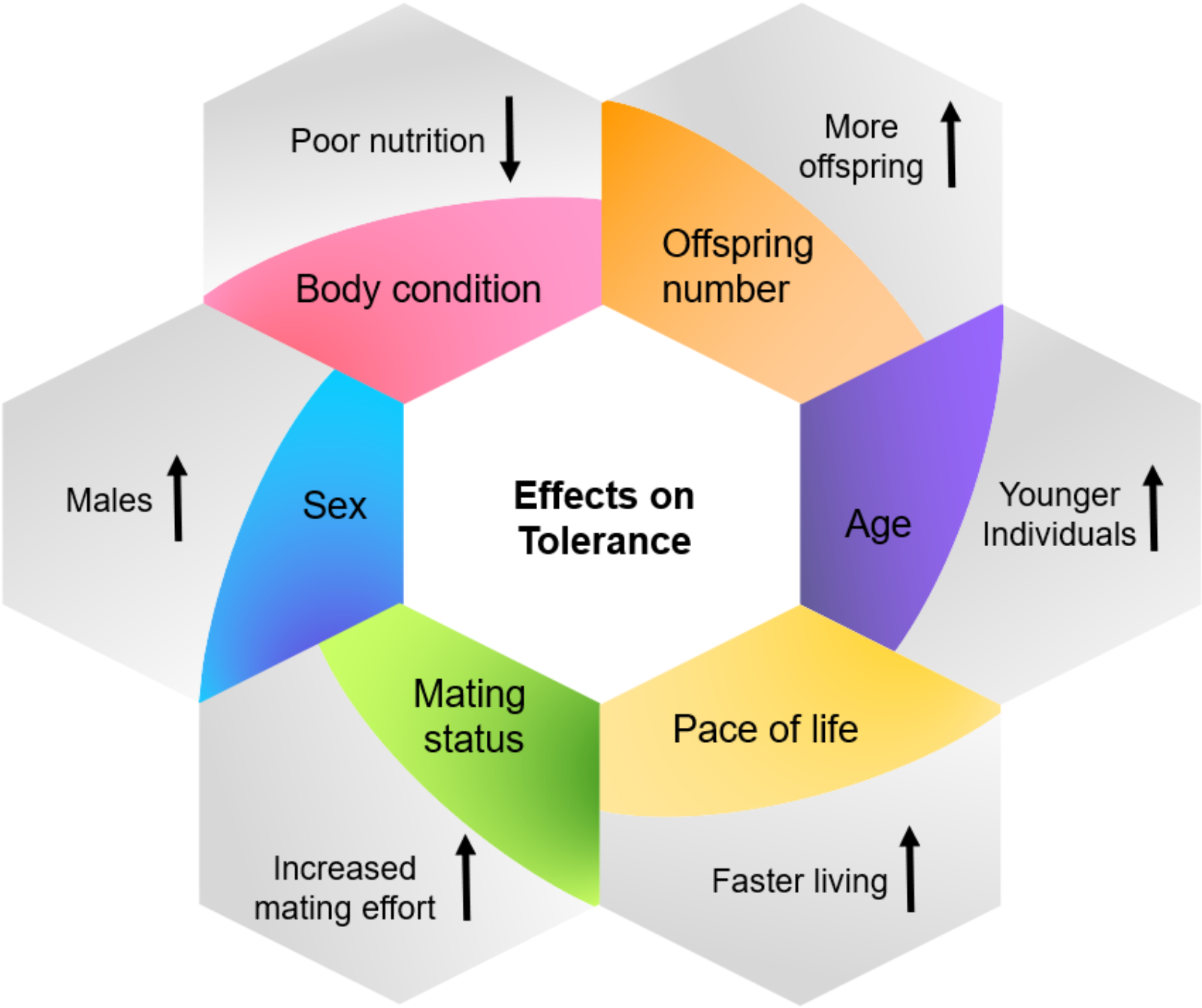
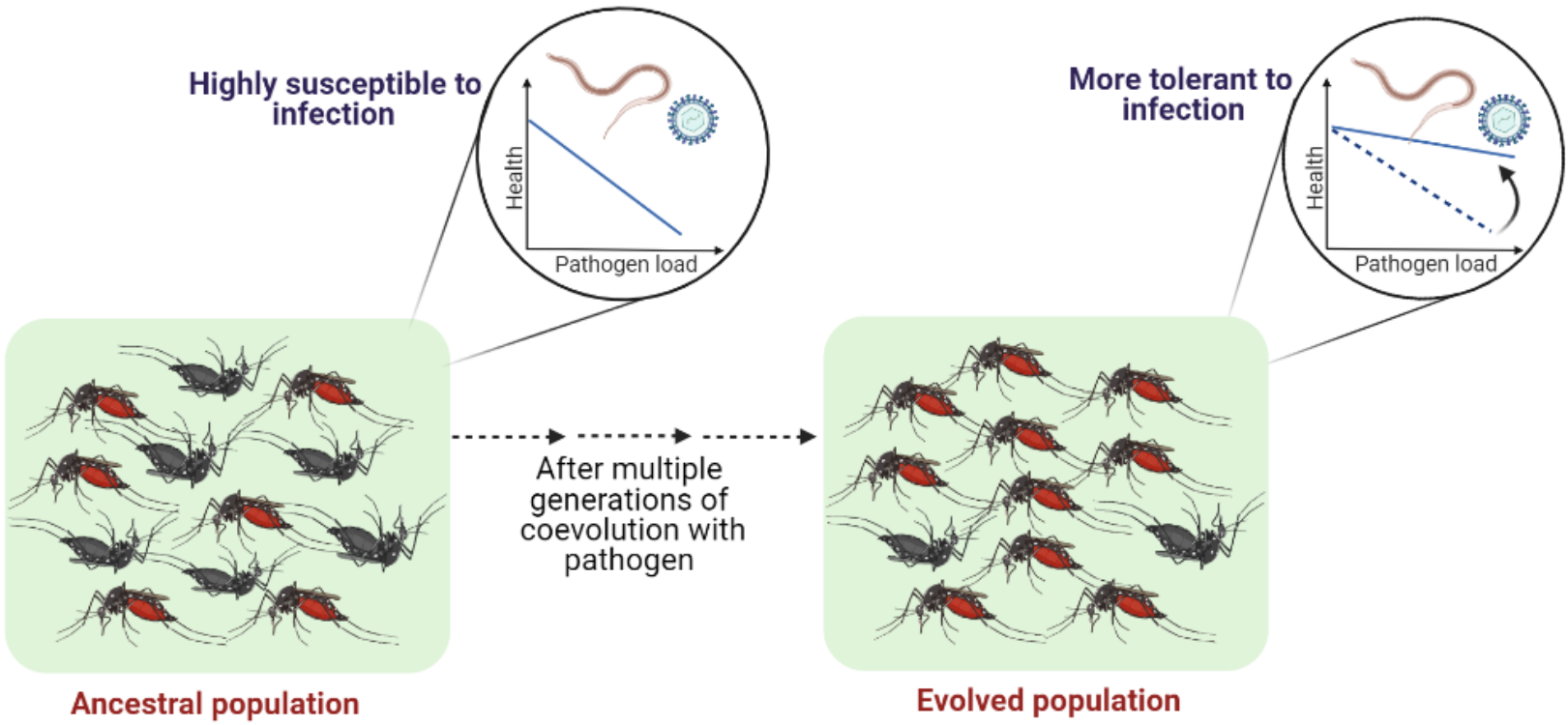

Resistance
Greater reduction in
average pathogen burden
Host fitness
High Resistance Genotype
Low Resistance Genotype
Pathogen Load
Tolerance
Greater reduction in fitness
at a given pathogen burden
Host fitness
High Tolerance Genotype
Low Tolerance Genotype
Pathogen Load


Features of Tolerance
Selection at viral coat proteins & host-receptor interface
Lower levels of proinflammatory cytokines
Step 1
Long-term host-pathogen coevolution
Immnuomodulatory mechanisms (e.g., stable regulatory T cell response)
Step 4
Pathogenic in novel hosts
Over-reactive immunity with high cytotoxic effects (e.g., cytokine storm)
Prolonged infectious period
Step 2
Increase in genetic diversity
Mutation
Genetic exchange
Step 3
Novel pathogen variant with higher transmission potential and spillover risks
Novel pathogen variant


Linking evolution of tolerance and new infections
Suggestion 1. Identify the plausible ecological niches for emerging infectious diseases
How do species interactions vary across geographical locations/ land-use types?
What are the potential reservoir species closer to human/ domestic animal populations?
What are the circulating zoonotic pathogens?
- What is the species and genetic diversity of circulating pathogens?
Suggestion 2. Explain the variations in pathogen prevalence data
What are the characteristic life-history traits of an effective reservoir host?
(e.g., age, sex or pace-of-life)
How do life-history traits affect immune strategies?
- Are there any trade-offs?
What are the immune strategies of an effective reservoir host?
- Do they show reduced inflammatory responses?
- Are they more tolerant to pathogens?
Does tolerance increase pathogen diversity, infectious period & transmission?
Suggestion 3. Identify the host-pathogen coevolutionary dynamics to predict emerging infection
- Is there stronger positive selection in reservoir hosts coevolving with pathogens?
- Is there more polymorphism in reservoir host receptors and pathogen derived molecules?
Suggestion 4. Set up controlled 'proof-of-principle' laboratory coevolution studies to test hypotheses generated in the wild and provide mechanistic insights
- Comparative analyses of natural populations to estimate variation in tolerance
- Experimental evolution to quantify whether stronger or de novo tolerance can evolve
- Genetic basis of adaptive evolution


Poor nutrition
More offspring
Body condition
Offspring number
Males
Sex
Effects on Tolerance
Age
Younger Individuals
Mating status
Pace of life
Increased mating effort
Faster living


Highly susceptible to infection
Health
Pathogen load
More tolerant to infection
Health
Pathogen load
After multiple generations of coevolution with pathogen
Ancestral population
Evolved population