Experimental infections reveal unexceptional viral tolerance in bats

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Abstract

Bats are a conspicuous source of zoonotic viruses with pandemic potential. A common explanation for bats being 'special' viral reservoirs is their ability to coexist with viruses without suffering overt disease. This assumption has catalyzed extensive research into the nature of bats as viral reservoirs and aspirations to develop novel therapeutics for humans based on unique features of bat immune systems that endow bats with broad viral tolerance. Surprisingly, the ubiquitous belief that bats evolved generalized viral tolerance mechanisms derives from relatively few well studied host-virus interactions rather than comprehensive analysis of globally available data. Here, synthesizing eighty-six years of experimental infections, involving 54 viruses, 85 host species, and over 5,600 individuals, we show that viral tolerance in bats appears unexceptional, with severe disease following inoculation by taxonomically diverse viruses, including ones that are relatively benign in humans. Bats' ability to prevent or limit the extent of clinical disease was indistinguishable from rodents, another prominent zoonotic reservoir for which major life history differences were hypothesized to select for contrasting antiviral strategies. We demonstrate that infection outcomes are instead shaped by experimental design, viral host range, and evolutionary context, suggesting that bats respond to novel infections similarly to other host groups. Our results question the idea that bats possess a 'one size fits all' solution wherein distinctive immune features protect against a wide variety of viruses. Instead, these features are likely to either have evolved from prolonged evolutionary interactions with specific viruses or to be evolutionarily unique but not determinants of disease outcomes across diverse viruses. Developing future biomedical translations of bat immunity and identifying life history traits which predispose host species to carry high consequence zoonoses is likely to require a nuanced understanding of specific host-virus interactions.

The purported rarity of overt disease in bats infected with viruses that are pathogenic in other mammals has fueled the widespread perception that bats have enhanced capabilities to limit the severity of viral infections, perhaps as a byproduct of adaptations to the energetic demands of flight (Baker et al., 2013; Brook and Dobson, 2015; Calisher et al., 2006; O'Shea et al., 2014; Shen et al., 2010; Wang et al., 2011; Wong et al., 2007). Efforts to explain putatively enhanced tolerance have identified numerous features of bat immune systems that appear to differ from other mammals (Banerjee et al., 2020; Irving et al., 2021; Morales et al., 2025). However, whether immune features are functionally linked to viral tolerance at the organismal level and whether tolerance mechanisms provide generalized protection against viruses remains largely unknown. Enticingly, if unique aspects of bat immune systems evolved as a byproduct of bat life history rather than adaptation to specific viruses, they might protect against diverse viruses (Baid et al., 2024; Dolgin, 2023; O'Shea et al., 2014; Shen et al., 2010). Broadly heightened tolerance may in turn select for greater pathogenicity, potentially explaining the elevated human case-to-fatality ratios of bat viruses (Brook et al., 2023; Guth et al., 2022). On the other hand, as neither taxon-specific immune features nor sub-clinical infections are unique to bats, viral tolerance in bats may reflect more conventional adaptations to the specific viral groups with which bats co-evolved (Shaw et al., 2017; Farrell and Davies, 2019).

Distinguishing whether bats exhibit more potent or taxonomically comprehensive viral tolerance compared to other mammals underpins research into the therapeutic potential of bat immune systems and the nature of bats as special zoonotic reservoirs. Observations of infection outcomes in wild bats are largely anecdotal; for example, viruses detected following mortality events with unknown etiology, or viruses detected in apparently healthy bats whose ultimate fates are unobservable (Kemenesi et al., 2018; Kohl et al., 2020). Field observations are further complicated by the small body sizes and cryptic life histories of bats, which likely limit detections of virus-induced morbidity and mortality to the most conspicuous events. In contrast, experimental inoculations of captive bats can confidently monitor infection outcomes and have revealed suprising tolerance to several viruses that can cause high mortality in humans (e.g., Marburg virus, Nipah virus) (Calisher et al., 2006; Baker et al., 2013; Guth et al., 2022). However, systematic comparisons across a broader range of viruses are required to determine whether these observations of tolerance represent the exception or the rule.

We examined the current state of evidence that bats have heightened viral tolerance by synthesizing eighty-six years of data on experimental viral infections. We contrasted bats with rodents, another species-rich mammalian order with small body sizes (Upham et al., 2019) that hosts a large number of zoonotic

viruses (some asymptomatically, (Pereira et al., 2023)). However, rodents have shorter life expectancies and higher reproductive rates than bats (Luis et al., 2013), in theory making them less likely to evolve tolerance to viral infection (Albery and Becker, 2021; Hayman, 2019; Han et al., 2015; Luis et al., 2013).

Beyond intrinsic host properties, virulence (reductions in host fitness due to infection) may arise from characteristics of viruses, such as the degree of host specialism and their co-evolutionary association with inoculated hosts (Galen et al., 2022; Leggett et al., 2013; Agueldo Romero and Elena, 2008). For example, viruses that infect a broader diversity of host species may replicate poorly in any single species, making them less pathogenic than host-specific viruses (Antonovics et al., 2013; Leggett et al., 2013). Host-virus co-evolution may also select for specific tolerance mechanisms which increase virulence in novel hosts which lack these defenses, or alternatively viral fitness may be reduced in novel hosts due to poor adaptation (Antonovics et al., 2013; Leggett et al., 2013). Our dataset included viruses that both co-evolved with bats and that were historically unlinked to bats, enabling us to assess whether tolerance reflects conventional coevolutionary predictions or whether bats have unique antiviral mechanisms leading to generalized tolerance across viruses. We therefore included measures of viral host range and co-evolution with host groups along with methodological details of experiments when comparing tolerance in bats and rodents. Finally, we investigated the relationship between human case fatality rates and disease outcomes in experimentally inoculated bats and rodents to assess whether either host group was systematically inoculated with viruses that are more pathogenic in a third host group, and to test the suggestion that bats generally tolerate viruses that are fatal in humans.

Diverse viruses cause overt disease in bats and rodents

We identified 112 studies published between 1936 – 2022 reporting disease outcomes following experimental inoculations (S1.1.6) of 54 viruses from fifteen viral families (53 RNA viruses; 1 DNA virus) into 85 susceptible host species (Figs. 1, S8; Table S3). These represented 149 host-virus pairs and a total of 5,622 inoculated individuals. We excluded laboratory-bred rodents as they may lack the full immune competency of their wild counterparts (Abolins et al., 2017). Across host-virus combinations, bat-virus pairs included a larger number of viruses than rodent-virus pairs, but fewer bat species were subjected to experimental inoculation (Fig. S9). Our dataset comprised a phylogenetically representative sample of both bats and rodents (Fig. S8), capturing variation in host life history traits (Fig. S10) hypothesized to influence tolerance (Hayman, 2019).

To avoid confounding resistance (i.e., the capacity to inhibit infection upon exposure) and tolerance, we restricted our analysis to studies in which authors deemed hosts as susceptible to infection and reported infection outcomes, including clinical and subclinical pathologies (S1). For each host-virus pair per study we converted reported disease outcomes into a five point scale ranging from no overt disease to death (S1.2). Across this dataset, disease occurred in 48% (40/83) of rodent-virus pairs and 73% (48/66) of bat-virus pairs (Fig. 1). Viruses from fifteen families caused disease (Table S5), with severe disease observed across the host phylogeny rather than being clustered within select clades (Fig. 1).

No difference in disease presence, mortality, or severity between bats and rodents

Although raw data indicated no clear difference in disease outcomes across host orders (Fig. 1), this comparison does not control for differences in experimental design (e.g., dose, inoculation route, number of animals inoculated, etc.), host-virus co-evolution, or the non-independence among taxa due to shared evolutionary histories. Indeed, the number of individual bats per study tended to be higher and more variable than the number of rodents (bats: median = 14.5, range 1 – 493; rodents: median = 6, range = 1 – 61), which could inflate observations of clinical disease in bats. We therefore used hierarchical Bayesian models to examine host taxonomic effects alongside eco-evolutionary metrics reflecting the potential degree of virus adaptation to inoculated hosts and the details of experimental design. At the host species level (i.e., the occurrence or maximum severity of disease among all individuals inoculated with a given virus within a given study; n=193 unique host-virus-study combinations, see S1.4), disease presence, mortality, and severity following viral inoculation remained indistinguishable between bats and rodents (the 80% credible interval for the effect of host order included zero; Fig. 2). The absence of host order effects was robust to removing Lyssaviruses, which represented 23% (45/193) of host-virus-study combinations in our dataset and, due to causing mortality, are sometimes considered the "exception to the rule" regarding viral tolerance in bats (Hayman, 2019) (See S2.2.4). In contrast, hierarchical effects describing non-independence among hosts and viruses indicated that variation in disease outcomes was in part driven by variation among hosts and viruses unexplained by other predictors in the model (S2.4). We also detected a strong influence of experimental design, with all metrics of disease positively associated with the number of inoculated individuals, pointing to the possibly that experimental infection studies have often been underpowered to detect disease.

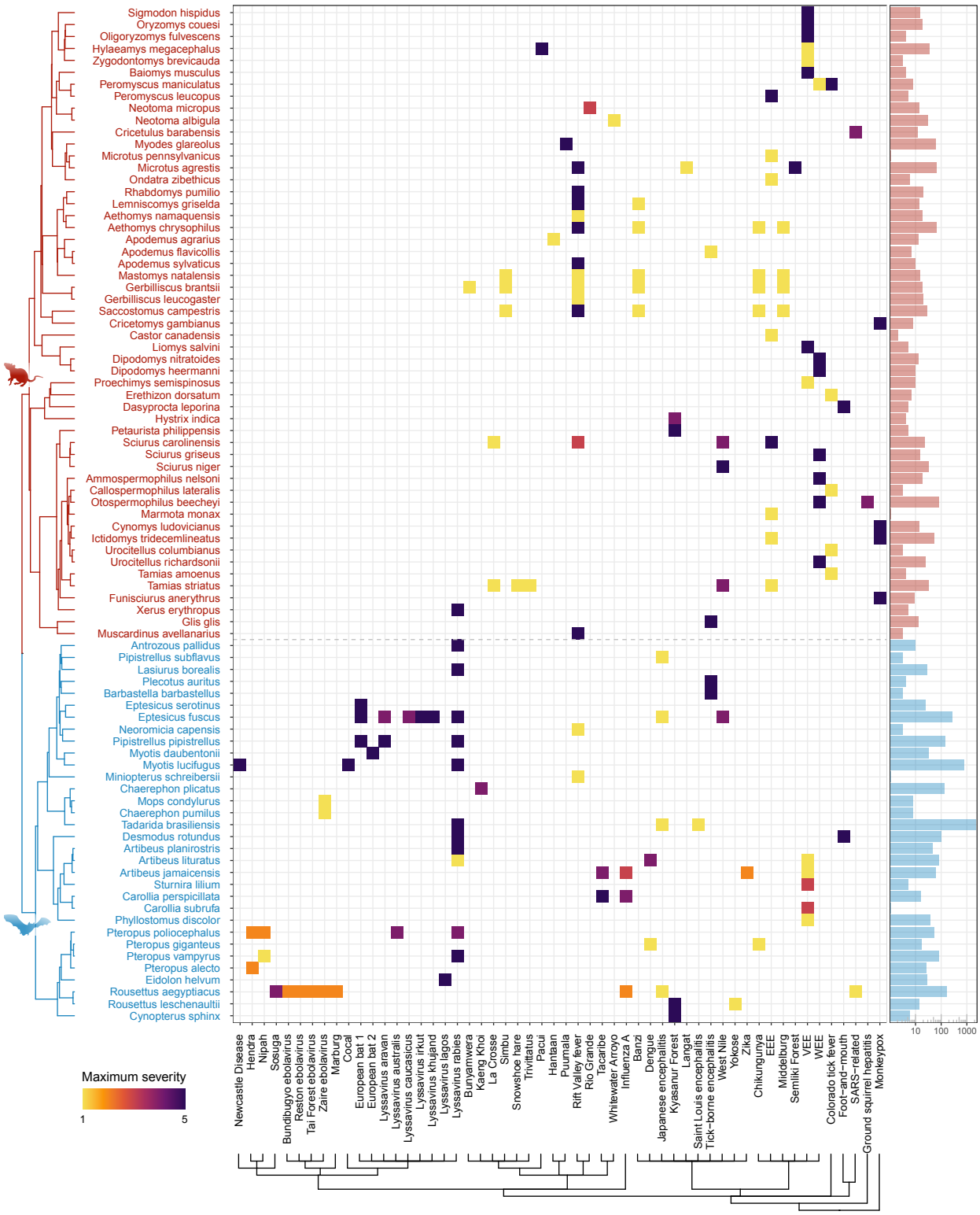

Figure 1: Maximum disease severity observed in experimental infections for each host-virus combination. The severity scale is calculated based on author reports of infection-induced disease and death (see S1.1.6 and S1.2.6 for details). Severity ranges from 1 (no disease) to 5 (mortality). Blank spaces indicate untested interactions. Hosts (rows) are grouped according to the Upham et al. (2019) mammal supertree. Viruses (columns) are grouped following the ICTV taxonomy. The barchart on the right shows the total number of host individuals per species included in experimental infections.

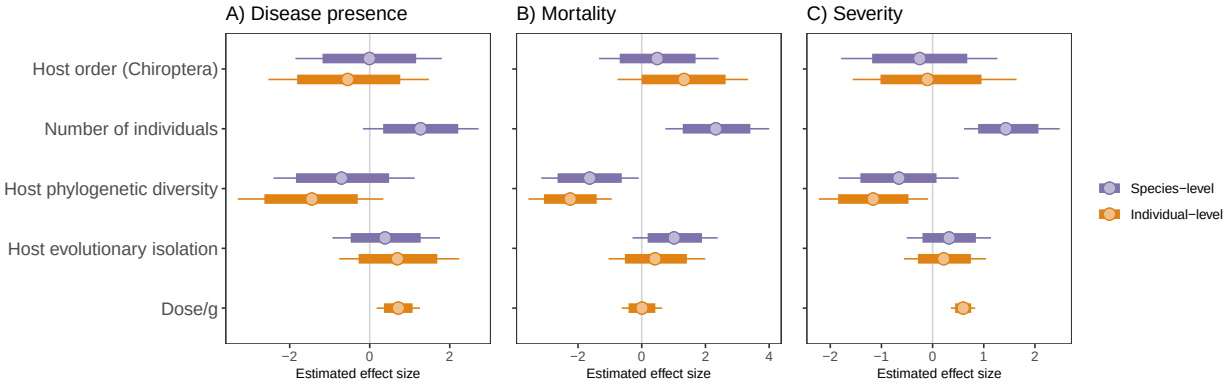

Figure 2: Estimated effect sizes for predictors in species-level and individual-level models of A) disease presence, B) mortality, and C) disease severity. Points represent posterior mean estimates, thick bars represent 80% credible intervals, thin bars represent 95% credible intervals. Predictors in both species- and individual-level models include host order (effect of Chiroptera with Rodentia as reference group), the standardized effect size of phylogenetic distance among all documented hosts per virus ("Host phylogenetic diversity"), the mean evolutionary distance from all documented host species to the inoculated host species ("Host evolutionary isolation"), and phylogenetic and non-phylogenetic hierarchical effects for host and virus species (S2.4). Species-level models additionally included the number of individuals per study ("Number of individuals") and a hierarchical effect of article. Individual-level models additionally included inoculation dose adjusted for species body mass ("Dose/g") and hierarchical effects for inoculation route (e.g. direct inoculation into the brain, oronasal inoculation etc.) and the dose unit measurement (e.g. Mouse LD50, TCID50, PFU, etc.). Positive host order effects would indicate more severe disease in bats compared to rodents.

Modeling host-virus interactions at the species-level allowed us to maximize the diversity of hosts and viruses in our analyses by including studies that did not report data for individual animals. However, this approach disguised individual-level variation in disease outcomes and required omitting experimental conditions that varied within studies (e.g., dose and inoculation route). We therefore analyzed infection outcomes for 1,620 individual animals, spanning 44 viruses, 75 host species, and 128 host-virus pairs from 84 studies which reported sufficiently resolved data. Using a similar structure to our species-level models, we fit individual-level models for the three measures of disease outcome, but replaced the study-level continuous predictor (number of host individuals) with body mass-corrected dose and inoculation route (see S1.2). These models again found no systematic difference in the occurrence of disease, infection-induced mortality, or disease severity between bats and rodents (Fig. 2). Unsurprisingly, larger inoculation doses increased the probability of disease and led to more severe disease with mean effect sizes comparable to eco-evolutionary predictors when predicting disease presence and severity (Fig. 2). Inoculation doses ranged over six orders of magnitude in both groups (Figs. S4, S6), but were not significantly different between bats and rodents (Fig. S7), suggesting that our failure to detect heightened tolerance in bats could not be explained by system-

atic differences in dose and inoculation route among bats and rodents (Figs. 2, S4, S5, S7). We also found no evidence that phylogenetic- or trait-based biases in species that were included in experimental infections could explain the absence of host taxonomic effects (Figs. S8, S10).

Contexts of infection rather than host order shape disease outcomes

Among eco-evolutionary metrics, infection by phylogenetic generalists (i.e., viruses that infect evolutionarily diverse host species) was less likely to result in disease, mortality, and severe disease (Fig. 2), consistent with the hypothesis that costs of generalism lead specialist viruses to cause more severe disease (Leggett et al., 2013). To explore whether the degree of host-virus co-evolution drives variation in disease outcomes, we included an effect of host evolutionary isolation (HEI) (Farrell and Davies, 2019), calculated as the mean phylogenetic distance from all known hosts to the inoculated host (see S1.2.4 for details).

Although estimated effect sizes showed high uncertainty, HEI tended to be positively associated with disease severity (Fig. 2), indicating that virus inoculations into distant relatives of other documented hosts are more likely to result in overt disease and more severe disease, mirroring a pattern observed for infection-induced mortality in humans (Guth et al., 2019) and domesticated animals (Farrell and Davies, 2019). As HEI does not differentiate whether documented host species are reservoirs to which the virus may be adapted or incidental hosts, we fit sensitivity models using a smaller dataset of 36 viruses with known reservoir host groups (Mollentze and Streicker, 2020). This allowed us to confidently assign inoculated hosts as belonging to the same (homologous) or a different (heterologous) order than the established reservoir host. Inoculations into homologous hosts were associated with greater disease presence and severity, but only for individual-level models (S2.2.2). Further, re-fitting our disease outcome models to heterologous infections only resulted in estimated effects in a consistent direction compared to full models, but with greater uncertainty, likely resulting from decreased sample sizes (S2.2.3). Taken together, our species- and individual-level models suggest that specialist viruses cause more severe disease and that overt disease is more likely in hosts that are evolutionarily divergent from those that a virus infects in nature.

Comparing disease severity among bats, rodents, and humans

Using human case fatality rates (CFR; Guth et al., 2022) as a comparable measure of pathogenicity, we next evaluated whether inoculation of bats with disproportionately pathogenic viruses could have disguised true

differences in tolerance relative to rodents. As expected from the generally elevated CFRs of bat-associated zoonotic viruses (Guth et al., 2022), experiments involving bats more often used viruses with higher human CFRs compared to experiments involving rodents (Fig. S21A). However, this putative host order effect disappeared when virus-level hierarchical effects were included, when we restricted our analysis to heterologous inoculations, and when bat-associated viruses were excluded (Fig. S23). As such, if genuinely heightened tolerance was undetectable in our dataset due to biases in viruses selected for experiments, it would mostly reflect bats experiencing less than expected disease from bat-associated viruses – consistent with the expectation that evolutionary association leads to virus-specific adaptations.

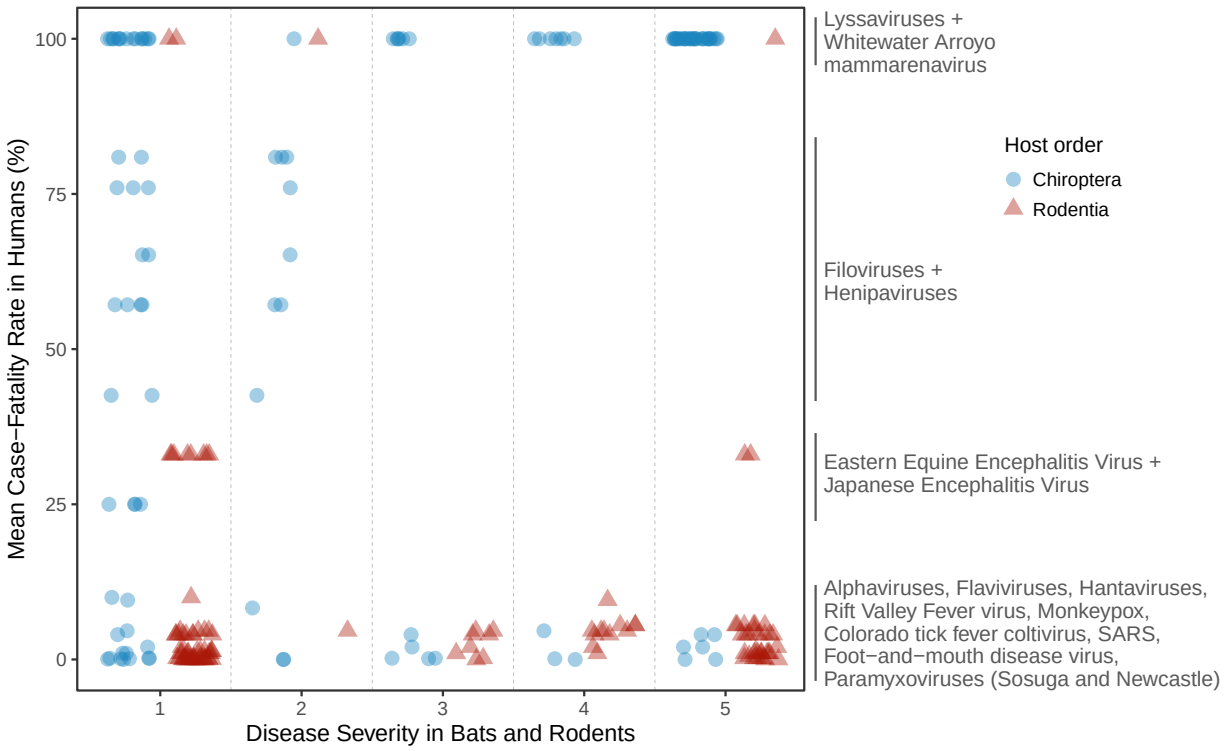

Figure 3: Mean human case fatality rates per virus versus maximum observed disease severity per experimental infection study. Colors and shapes indicate the taxonomic order (Chiroptera / Rodentia) of host species in the experimental infection data. See Fig. S22 for an alternate version indicating the taxonomic group of known reservoir hosts. Points are jittered horizontally to improve visibility of overlapping points.

We next related CFRs with disease outcomes in experimentally inoculated animals to examine whether bats consistently tolerate viruses that cause severe disease in humans (Fig. 3). Supporting this notion, we identified a region of putatively heightened tolerance where viruses cause high mortality in humans but mild disease in bats. However, closer examination revealed that this region was represented only by

the Filoviruses and Henipaviruses, which are strongly bat-associated (Fig. S22). More surprising, non-bat-associated viruses which cause relatively low human mortality (i.e., Flaviviruses, Alphaviruses, and Hantaviruses; CFRs $<20\%$), sometimes caused severe disease in bats, including mortality (severity scores of 5; Fig. 3). Disease outcomes in bats are therefore compatible with conventional expectations that vertebrate immune systems are tuned to tolerate co-evolved viruses, but that these defenses fail to reliably protect against evolutionarily novel viruses (Farrell and Davies, 2019; Poulin and Combes, 1999). In both bats and rodents, inoculations of moderate to high human CFR viruses from heterologous hosts were virtually absent (Fig. S22), highlighting the currently weak comparative basis for claims of exceptional tolerance.

Discussion

The entrenched belief that bats have evolved unique mechanisms to tolerate viruses more effectively than other animals prompted discoveries of features of bat immune systems which are proposed to have translational medical value (Baid et al., 2024; Banerjee et al., 2020; Irving et al., 2021). Synthesizing eighty-six years of experimental infections, we show that a wide diversity of viruses cause severe disease in bats and find no evidence for systematic differences in tolerance between bats and rodents, a prominent zoonotic reservoir clade with contrasting life history strategies to bats. Instead, disease outcomes are shaped by factors which would be expected in any vertebrate, including aspects of experimental design, the host specificity of viruses used, and the degree of co-evolutionary association with the inoculated host. Observed viral tolerance in bats is therefore more likely to reflect virus-specific co-evolved defenses against bat viruses than broad-acting antiviral immune traits which may have therapeutic value against viruses in general.

Our results, constituting the first quantitative test of whether bats have exceptional viral tolerance, support the idea that bats are unlikely to possess a ‘one size fits all’ solution where life-history driven selection resulted in generalized viral tolerance (Pei et al., 2024). If unique traits of bats (increased longevity given body size, flight) led to the evolution of unique antiviral traits, our results suggest that these are either insufficient to protect bats at the organismal level (versus effects observed in vitro) or only protect against certain viruses. We speculate that beliefs in exceptional viral tolerance became embedded due to the association of bats with viruses highly pathogenic in humans (Guth et al., 2022), the challenges of observing virus-induced mortality in most bat species which are small bodied and roost reclusively, and an extrapolation of theory founded on a small set of well studied systems (Calisher et al., 2006; Baker et al., 2013), such as Henipaviruses and Marburg virus (Williamson et al., 1998; Guito et al., 2021).

Exploiting published experimental infections provided a unique opportunity to test theories on viral tolerance, but introduced several challenges. While we adjusted for variation in experimental design choices such as dose and inoculation route in our models of disease outcomes, other important features of experimental design, such as the degree of prior viral passage may have degraded adaptations necessary for successful natural infections. Our study was also limited to bats and rodents. While these mammalian groups are commonly used in experimental viral infections and host the majority of viral zoonoses (Mollentze and Streicker, 2020), the omission of other host clades opens the possibility that both bats and rodents have unusually high viral tolerance. However, given that the life history strategy of rodents prioritizes reproduction over longevity (Albery and Becker, 2021; Hayman, 2019; Han et al., 2015; Luis et al., 2013), and mechanisms that limit the severity of viral infections in bats are suggested to be byproducts of adaptations to powered flight (Baker et al., 2013; Brook and Dobson, 2015; Calisher et al., 2006; O'Shea et al., 2014; Shen et al., 2010; Wang et al., 2011; Wong et al., 2007), this outcome seems unlikely. Although our results should be re-visited as inoculations into other host orders accumulate, we suggest that bats and rodents are well characterized groups that represent broader phenomena of taxon-specific immunological traits (Shaw et al., 2017) and context-dependent outcomes of host-virus interactions. It is also conceivable that certain bat clades have heightened tolerance or susceptibility to viruses, akin to results observed in experimental infections of invertebrates (Longdon et al., 2015; Imrie et al., 2024). While the hierarchical effects of bat species in our models of disease outcome do not obviously support this conclusion (S2.4), we caution that sparse data for some bat clades makes these effects difficult to interpret. Finally, the ideal test of generalizable viral tolerance would have inoculated bats and rodents with the same sets of viruses, comprising both those that are homologous and heterologous. Unfortunately, such experiments remain rare: only 13 out of 54 viruses were inoculated into both bats and rodents. This limitation reinforces the current limited evidence for any unique and generalisable tolerance to viral infection in either clade.

Implications for future research

The absence of evidence for generalized tolerance to viruses raises doubts that broad spectrum antivirals could be developed from unique features of bat immune systems. Virus-specific tolerance identified through investigation of a broader diversity of host-virus interactions – particularly those representing long term co-evolution – may be more likely to yield useful therapeutics targeted to particular viral clades. Given that the current state of evidence suggests that the phenotype of exceptional tolerance either does not exist, has

insufficient data to be robustly quantified, or is limited to viruses where tolerance likely reflects conventional co-evolutionary processes, investigations into bats' "exceptional" viral tolerance should be considered cautiously. Looking forward, it will be important to identify how specific immunological traits protect across related viruses and, if some host taxa show heightened viral tolerance, to determine which viruses their immune features may suppress. To this end, we identify major evidence gaps in the current body of experimental inoculations: few bat-associated viruses have been inoculated into rodents, rodent-associated viruses with moderate human CFR have not been inoculated into bats or wild rodents, and relatively few human-associated viruses have been inoculated into either bats or rodents (Fig. S22). The influence of inoculation dose and study size on tolerance outcomes also implies that some observations of apparent tolerance may be artifacts of experiments that are not sufficiently powered to detect disease.

The surprising inconsistency between our results suggesting that tolerance in bats follows conventional evolutionary expectations and the pervasive notion of exceptional viral tolerance in bats emphasizes the need to enhance communication between virologists, immunologists, ecologists, and evolutionary biologists interested in the relationships between bats and viruses. In particular, we urge comparisons of bats and other taxa to use analogous baselines (e.g., comparing bats and other wildlife rather than bats to humans or laboratory animals) and to incorporate robust quantitative consideration of host phylogeny, virus phylogeny, and co-evolutionary associations in order to differentiate case-specific outcomes with generalizable conclusions. The recurrent emergence of high impact zoonoses from bats, including ebolaviruses, henipaviruses, and coronaviruses makes the need to study the relationship between bats and viruses unquestionable. Nevertheless, our study, together with recent work countering theories that viral diversity in bats is unusual, that the zoonotic propensity of bat viruses is elevated, and that bats might not mount functional adaptive immune responses, raises further doubts on the distinctiveness of bats as viral reservoirs and encourages greater consideration of the context dependency of bat-virus interactions (Mollentze and Streicker, 2020; Guy et al., 2019; Jebb et al., 2020; Kessler et al., 2024).

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Data & Code Accessibility

Data and scripts to reproduce analyses are available at https://github.com/maxfarrell/bat_rodent_tolerance and archived at Zenodo (Farrell et al., 2025).

Author Contributions

Conceptualization: D.S. and M.J.F.; Methodology: M.J.F, N.M, and D.S.; Data compilation: M.J.F. and S. T.; Data analysis: M.J.F.; Visualization: M.J.F.; Funding acquisition: D.S. and M.J.F.; Supervision: D.S.; Writing – original draft: M.J.F.; Writing – review and editing: M.J.F., D.S., and N.M.

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