

1 **Bats host the most virulent—but not the most dangerous—zoonotic viruses**

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## 37 **Abstract:**

38 Identifying virus characteristics associated with the largest public health impacts on human  
39 populations is critical to informing zoonotic risk assessments and surveillance strategies. Efforts  
40 to assess “zoonotic risk” often use trait-based analyses to identify which viral and reservoir host  
41 groups are most likely to source zoonoses but have not fully addressed how and why the impacts  
42 of zoonotic viruses vary in terms of disease severity (‘virulence’), capacity to spread within  
43 human populations (‘transmissibility’), or total human mortality (‘death burden’). We analyzed  
44 trends in human case fatality rates, transmission capacities, and total death burdens across a  
45 comprehensive dataset of mammalian and avian zoonotic viruses. Bats harbor the most virulent  
46 zoonotic viruses even when compared to birds, which alongside bats, have been hypothesized to  
47 be “special” zoonotic reservoirs due to molecular adaptations that support the physiology of  
48 flight. Reservoir host groups more closely related to humans—in particular, Primates—harbor  
49 less virulent, but more highly transmissible viruses. Importantly, disproportionately high human  
50 death burden, arguably the most important metric of zoonotic risk, is not associated with any  
51 animal reservoir, including bats. Our data demonstrate that mechanisms driving death burdens  
52 are diverse and often contradict trait-based predictions. Ultimately, total human mortality is  
53 dependent on context-specific epidemiological dynamics, which are shaped by a combination of  
54 viral traits and conditions in the animal host population and across and beyond the human-animal  
55 interface. Understanding the conditions that predict high zoonotic burden in humans will require  
56 longitudinal studies of epidemiological dynamics in wildlife and human populations.

## 57 **Significance statement:**

58 The clear need to mitigate zoonotic risk has fueled increased viral discovery in specific reservoir  
59 host taxa. We show that a combination of viral and reservoir traits can predict zoonotic virus  
60 virulence and transmissibility in humans, supporting the hypothesis that bats harbor  
61 exceptionally virulent zoonoses. However, pandemic prevention requires thinking beyond  
62 zoonotic capacity, virulence, and transmissibility to consider collective ‘burden’ on human  
63 health. For this, viral discovery targeting specific reservoirs may be inefficient as death burden  
64 correlates with viral, not reservoir, traits, and depends on context-specific epidemiological  
65 dynamics across and beyond the human-animal interface. These findings suggest that  
66 longitudinal studies of viral dynamics in reservoir and spillover host populations may offer the  
67 most effective strategy for mitigating zoonotic risk.

## 68 **Introduction**

69 The vast majority of human pathogens are derived from animal populations (1). In response to  
70 increasingly frequent zoonotic spillovers and their substantial public health risks (2), there has  
71 been a movement to identify the ecological systems and taxonomic groups of animals and  
72 pathogens that are most likely to source the next emerging zoonosis in the human population (3–  
73 9). However, most of this work has centered on a binary definition of zoonotic risk—whether  
74 particular pathogens are capable of infecting humans—without considering how pathogens vary  
75 with respect to their impacts on humans after spillover. The ongoing SARS-CoV-2 pandemic has  
76 re-emphasized the reality that not all zoonoses pose risks of equal magnitude—some are  
77 exceptionally more dangerous than others due to the severity of disease they cause (‘virulence’)  
78 or their capacity to spread within human populations (‘transmissibility’), which combined,  
79 influence the total number of human deaths (‘death burden’) (10). Given the extraordinary  
80 diversity of both animal hosts and the viruses they harbor, understanding which animal and virus

81 groups are more likely to source dangerous zoonoses is an important public health aim. Many  
82 high-profile zoonotic viruses—including Nipah and Hendra henipaviruses; Ebola filovirus;  
83 SARS, MERS, and SARS-CoV-2 coronaviruses; pandemic avian influenzas; West Nile virus;  
84 and Eastern Equine encephalitis virus—have emerged from Chiropteran (bat) or avian reservoirs  
85 (11). The high number of zoonotic viruses found in bats and birds has been attributed to their  
86 large gregarious populations, mobility, ability to colonize anthropogenic environments, and sheer  
87 species diversity (7, 11). Nonetheless, the question remains: are bat- and/or bird-borne viruses  
88 disproportionately dangerous?

89 A recent meta-analysis (10) found that mammalian reservoir hosts most closely related to  
90 humans harbor zoonoses of lower impact in terms of mortality relative to more phylogenetically  
91 distant hosts. These results were consistent with phylogenetic trends in virulence that have been  
92 reported in cross-species pathogen emergences in other systems (12, 13), and likely reflect  
93 mismatches in host biology, physiology, and ecology. Notably, order Chiroptera (bats)—one of  
94 the more distantly related host orders—had the highest positive effect size on case fatality rate in  
95 humans. Nevertheless, this analysis considered only directly transmitted viruses and viruses  
96 derived from mammalian hosts, despite the existence of several high-profile vector-borne and  
97 avian zoonoses (11). In particular, birds occupy a separate taxonomic class from humans—a  
98 phylogenetic distance that might correlate with heightened virulence in humans.

99 *In vitro* work has suggested that molecular adaptations that support the physiology of  
100 flight, a trait unique to bats among mammals, may allow bats to tolerate rapidly-replicating  
101 viruses that express heightened virulence upon emergence in less tolerant hosts such as humans  
102 (14)—thus offering a possible explanation for bat virus virulence. Bats and birds share a suite of  
103 convergent flight adaptations—both taxa are remarkably long-lived for their body size and  
104 appear to circumvent metabolic constraints on longevity through cellular pathways evolved to  
105 mitigate oxidative stress induced by flight (11). These metabolic adaptations are hypothesized to  
106 be linked to the evolution of virulent viruses in bats, but only typically discussed with respect to  
107 their effect on lifespan in birds (15). A few papers have reviewed birds' role as special zoonotic  
108 reservoirs (11, 16), but the virulence of avian zoonoses remains largely unexplored. Nonetheless,  
109 though the most virulent zoonotic viruses may garner the most publicity, these pathogens are not  
110 necessarily the most 'dangerous' to human health. Rather, human health is most impacted by  
111 viruses that cause large volumes of cases and deaths ('burden'). While some viruses such as  
112 Ebola and rabies are associated with both high case fatality rates and burden in the human  
113 population, pandemic viruses are often characterized by relatively low case fatality rates but high  
114 human transmissibility. The 2009 H1N1 influenza pandemic was estimated to have caused 60.8  
115 million cases and more than 12,000 deaths in the United States alone with a case fatality rate of  
116 less than 1% (17), and as of July 9<sup>th</sup>, 2021, SARS-CoV-2 has caused over 185 million cases and  
117 4 million deaths worldwide with a case fatality rate of just 2.2% (18). To prevent the next  
118 zoonotic pandemic, it is important to think beyond the individual measures of zoonotic capacity,  
119 virulence, and transmissibility to consider collective 'burden' on public health.

120 We apply generalized additive models (GAMs) to a comprehensive dataset of  
121 mammalian and avian zoonotic viruses to identify reservoir host and viral traits predictive of the  
122 (a) case fatality rate (CFR), (b) capacity for forward transmission, and (c) death burden induced  
123 by infections in the human population—with the goal of characterizing sources of zoonotic  
124 viruses that pose the greatest danger to global health. Our work builds on a small body of meta-  
125 analyses that have begun to explore variation in the virulence and between-human

126 transmissibility of zoonotic viruses (4, 19–21). We provide the most thorough analysis of  
127 quantitative zoonotic virus data published to date, including the first analysis of burden and the  
128 largest sample size—with trends examined across the majority of known zoonotic viruses. We  
129 hypothesized that birds—given their capacity for flight and phylogenetic distance from  
130 humans—might rival bats for the association with the most virulent zoonotic viruses. However,  
131 we did not expect bats or birds to be responsible for the greatest burden on global health, instead  
132 anticipating high burden to be largely a function of viral traits and associated with reservoir  
133 orders that harbor less virulent, more transmissible viruses.

## 134 **Results**

135 Drawing from existing databases (3, 7), we compiled a dataset of all mammalian and avian  
136 zoonotic virus species that met a strict definition of zoonotic—requiring a record of natural  
137 human infection confirmed by PCR or sequencing and animal-to-human directionality in  
138 transmission. Virus species linked to multiple independent reservoir groups (e.g., canine and bat  
139 rabies) or those which spillover to humans both directly from their reservoir and through bridge  
140 hosts (e.g., Nipah virus) were subdivided into separate entries for each unique transmission chain  
141 ending in spillover, creating a final dataset of 87 viruses with a total of 91 transmission chains  
142 (*SI Data and Results*, Table S1). We then applied generalized additive models (GAMs) to assess  
143 predictors (*SI Data and Results*, Table S7) of three metrics of zoonotic risk: global estimates of  
144 case fatality rates (CFRs) in humans (proxy for virulence), capacity for forward transmission  
145 within the human population ranked on a four-point scale (human transmissibility), and post-  
146 1950 cumulative death counts (death burden) (*Materials and Methods*).

147 **Predictors of human CFRs.** In our virulence analysis, we observed a left-skewed distribution of  
148 CFRs, with 34.1% of virus species linked to no fatalities (0% CFR) and more than half (58.5%)  
149 linked to a CFR of less than 10% (Figure S1 in *SI Figures*). Bat reservoirs harbored the most  
150 virulent zoonotic viruses, contributing two thirds of the identified viruses with CFRs higher than  
151 50%. The top selected GAM to predict global estimates of CFR in humans—across the 86  
152 unique zoonotic transmission chains for which at least two human cases have been recorded—  
153 explained 74.7% of the deviance and included virus family, reservoir host group, bridged  
154 spillover, and vector-borne transmission (Figure 1, Table S5a in *SI Data and Results*). Consistent  
155 with previous work (10) and the hypothesis that bats are “special” zoonotic reservoirs, order  
156 Chiroptera had the largest positive effect size on CFR in humans (Figure 1b). The top selected  
157 model predicted a CFR of 65.4% for zoonotic viruses derived from order Chiroptera,  
158 representing a more than 50% increase from the next highest predicted CFR (Figure S2).  
159 Contrary to our flight hypothesis, avian reservoirs were not similarly associated with  
160 disproportionately virulent zoonoses; order Aves had a neutral effect size on human CFR that  
161 was not significant. Order Cetartiodactyla had the largest negative effect size on CFR, but  
162 notably, Cetartiodactyl hosts in our dataset included only domesticated animal species—cattle,  
163 pigs, and camels. The long coexistence of domestic animals and humans likely facilitated  
164 increased research effort for this clade, which have may have led to greater detection of low  
165 virulence zoonoses in domestic animal species. A long history of domestic animal-human  
166 coexistence may also have supported the development of preexisting human immunity to some  
167 livestock diseases, resulting in lower virulence infections.

168 Past analyses have observed that particular viral families associate non-randomly with  
169 particular host groups (10, 22), suggesting that virus taxonomy may underlie trends in virulence  
170 across reservoir orders. For example, the high number of virulent bat-borne zoonoses (Figure S1

171 in *SI Figures*) may be entirely a result of the virus groups that preferentially infect bats, rather  
172 than the bats themselves. However, here, reservoir host group and virus family significantly  
173 predicted CFR within the same models (Figure 1a), indicating that both reservoir and virus taxa  
174 contributed to the observed variation in virulence. Chiroptera had the highest positive effect size  
175 on CFR despite being associated with virus families that ranged from the most (Rhabdoviridae)  
176 to least (Coronaviridae) virulent (Figure 1c). Removing the 100% fatal lyssaviruses (n=5) from  
177 the dataset resulted in large reductions in the CFR predicted for bat-borne zoonoses (Figure S4),  
178 though order Chiroptera still had the highest and most significant positive effect size on CFR  
179 (Figure S2 in *SI Figures*, Table S6a in *SI Data and Results*).

180 Previous work has demonstrated a positive correlation between reservoir host  
181 phylogenetic distance from humans and the case fatality rates of zoonoses derived from those  
182 reservoirs (10); in our analysis, however, reservoir host group phylogenetic distance from  
183 Primates was not correlated with CFR, dropping entirely from the top ranked model and not  
184 ranking significantly in any of the top 15 selected models (Figure 1a). The combined effect of  
185 reservoir host group and virus family as predictor variables in the same model likely  
186 overwhelmed any correlation between host phylogeny and CFR, particularly given the lack of  
187 granularity in our phylogenetic distance variable, based on a time-scaled phylogeny, which  
188 produced only six unique distance values across nine host groups, with Chiroptera and four of  
189 the other mammalian orders clustering at a single distance level (*Materials and Methods*).  
190 Nevertheless, trends in effect size on CFR (Figure 1b) and predicted CFR (Figure S2) across  
191 reservoir host groups suggest that, in general, virulence increases with phylogenetic distance, but  
192 this positive correlation may collapse at “extreme” distances.

193 To test whether these results held across a larger sample size, we ran a CFR analysis that  
194 included viruses that met a more lenient definition of zoonotic—specifically, viruses with only  
195 serological evidence of infection in humans, viruses that have only caused human infections in  
196 laboratory settings, and viruses for which only one human case has been recorded—increasing  
197 our dataset to 119 virus species with a total of 123 unique zoonotic transmission chains (Figure  
198 S5 in *SI Figures*, Table S6b in *SI Data and Results*). This supplementary analysis echoed the  
199 results from our first analysis of global CFR estimates—both reservoir and virus taxonomy  
200 contributed to the observed variation in CFR (Figure S5a in *SI Figures*); and Chiroptera had the  
201 highest positive effect size on CFR, whereas Aves had a neutral nonsignificant effect (Figure  
202 S5b in *SI Figures*).

203 To assess whether CFR trends might be influenced by health care differences among the  
204 virus’ differing geographic ranges, we tested whether Gross Domestic Product per capita  
205 (GDPPC) significantly predicted country-specific CFR estimates—calculated from death and  
206 case counts in countries that have reported the largest outbreaks of each given virus species, with  
207 up to three country estimates for each species for a total of 119 estimates across the 86 unique  
208 zoonotic transmission chains. First, we modeled all 119 country-specific CFR estimates  
209 separately to test whether GDPPC predicts country-level variation in CFR (Figure S6 in *SI*  
210 *Figures*, Table S6c in *SI Data and Results*). Although significant, GDPPC explained a low  
211 percentage of the deviance (Figure S6a in *SI Figures*), and wide confidence intervals indicated  
212 uncertainty in trends (Figure S6d in *SI Figures*). To gauge whether variation in GDPPC among  
213 virus’ geographic ranges might bias the trends in global CFR estimates observed in the Figure 1  
214 models, we then modeled GDPPC and country CFR estimates aggregated at the level of the 86  
215 unique zoonotic transmission chains (Figure S7 in *SI Figures*, Table S7d in *SI Data and Results*).

216 GDPPC was not significant in any of the top models, often dropping entirely during model  
217 selection (Figure S7a in *SI Figures*), suggesting that health care differences among the virus'  
218 geographic ranges most likely do not bias Figure 1 trends. Nevertheless, as with the  
219 supplementary analysis presented in Figure S5, both analyses of the country CFR estimates  
220 echoed all key results presented in Figure 1.

221 **Predictors of transmissibility within human populations.** We found that most zoonotic  
222 viruses (72.1%) have not been reported to transmit within the human population following  
223 spillover (i.e., transmissibility rank = 1, or  $R_0 = 0$ ) (Figure S8). Only 15.1% of virus species had  
224 demonstrated capacity for endemic transmission among humans, of which the majority (61.5%)  
225 were sourced from Primates. The top selected GAM to predict the ordinal rank of  
226 transmissibility within human populations—across the 86 unique zoonotic transmission chains  
227 for which at least two human cases have been recorded—explained 56.7% of the deviance and  
228 included virus family, the phylogenetic distance between each virus' reservoir host group and  
229 Primates, vector-borne transmission, and the virus species publication count (Figure 2, Table S5b  
230 in *SI Data and Results*). Transmissibility declined with phylogenetic distance from Primates, but  
231 the estimated trend was highly uncertain (Figure 2c). We therefore reran the analysis with  
232 reservoir host group as the only host taxonomic predictor (excluding the phylogenetic distance  
233 variable). This analysis identified Primates as the only host order significantly associated with  
234 heightened transmissibility in humans, suggesting that this group is the primary driver of the  
235 phylogenetic trend observed in the top selected model (Figure S9a in *SI Figures*, Table S6c in *SI*  
236 *Data and Results*).

237 Evolution of virulence theory typically assumes a tradeoff between virulence (death rate  
238 due to infection) and transmission rate on the basis that while high within-host growth rates  
239 increase infectiousness, they also increase damage to the host, increasing virulence and thus  
240 shortening the infectious period and reducing opportunities for future transmission (23, 24).  
241 Critically, CFR is not equivalent to virulence, but instead, a proxy that can be reliably quantified.  
242 As defined by Day 2002 (25), CFR is a function of both pathogen virulence ( $\alpha$ ) and clearance  
243 rate ( $\sigma$ ), in which  $CFR = \alpha / (\alpha + \sigma)$ . Thus, virulent pathogens (high  $\alpha$ ) with high clearance  
244 rates (high  $\sigma$ )—e.g., acute, short-lived infections such as Chikungunya virus (26)—could  
245 produce low CFRs. In contrast, less virulent pathogens (low  $\alpha$ ) with low clearance rates (low  
246  $\sigma$ )—e.g., persistent infections such as HIV (27)—could produce high CFRs. Nevertheless, in our  
247 data, we observed a relationship between CFR and transmissibility in humans that roughly  
248 supports the fundamental theoretical tradeoff between virulence and transmission rate (Figure  
249 S10 in *SI Figures*). Viruses causing the highest CFRs in humans (>75% CFR) clustered in the  
250 lower right corner with the lowest capacity for forward transmission in the human population,  
251 implying maladaptive virulence. Conversely, the least virulent viruses (0% CFR) clustered at  
252 either the lowest transmission capacity—likely indicative of poor compatibility with humans—or  
253 the highest transmission capacity—suggesting transmission uninhibited by virulence.

254 **Predictors of post-1950 death burden in the human population.** For our death burden  
255 analysis, we modeled the total number of deaths resulting from a given zoonosis recorded  
256 worldwide since 1950 (and up until March 7<sup>th</sup>, 2021). In cases where our death count could only  
257 begin after 1950, either because a zoonosis first emerged in humans after 1950 or because  
258 reliable death records were only available for a subset of the timeline, we standardized analyses  
259 by including an offset for the number of years over which the death counts were recorded. The  
260 raw death count distribution was highly left-skewed, with 39.5% of virus species linked to 0

261 deaths and more than half (62.7%) linked to fewer than 50 deaths (Figure S11 in *SI Figures*). We  
262 observed significant overdispersion in death counts, even when standardized by the number of  
263 years over which the deaths were recorded, with deaths per year ranging from zero to almost 2  
264 million for SARS-CoV-2. Just two viral predictors—virus family and species publication  
265 count—explained most of the variation in death burden among the 91 zoonotic transmission  
266 chains across all the top GAMs (Figure S12a in *SI Figures*). Host predictors explained a very  
267 low percentage of the variation in death burden across all the top selected models, often dropping  
268 entirely during term selection. Virus species publication count tempered virus family effects  
269 (Figure S12c in *SI Figures*) because virus species with high death burdens were also associated  
270 with high publication counts, likely because high death burdens motivate increased research  
271 efforts. In contrast, there was little evidence that poorly studied viruses had unusually low death  
272 burdens, implying that a lack of diagnostic effort is not a major driver of low death burdens in  
273 our data (Figure S12c in *SI Figures*). After excluding the virus species publication predictor, we  
274 found that Coronaviridae, Orthomyxoviridae and Rhabdoviridae had the highest positive effect  
275 sizes on death burden, driven by, respectively, the SARS-CoVs, the Influenza A transmission  
276 chains, and Rabies virus (Figure 3b, Table S5c in *SI Data and Results*). With virus publication  
277 count removed, the top four models included two reservoir traits—phylogenetic distance from  
278 Primates and species richness—as significant predictors. Reservoir groups most closely related  
279 to Primates were associated with heightened death burdens relative to more distantly related  
280 reservoirs, consistent with results from our transmissibility analyses that indicated that reservoirs  
281 most closely related to Primates harbored more transmissible viruses (Figure 3c). Reservoir  
282 species richness positively correlated with death burden, as we would expect given that species  
283 richness has been found to correlate with the number of viruses associated with a given reservoir  
284 order (Figure 3d) (7). However, both reservoir predictors explained a small fraction of the  
285 variation in death burden relative to virus family, confirming that death burden is largely a  
286 function of viral traits (Figure 3a).

287 While some reservoir groups—bats, primates, rodents, and birds—have sourced more  
288 high burden viruses than others (Figure 4a), both our model results and raw data suggested that  
289 high burden viruses appeared to be function of viral traits, not the reservoirs themselves. No  
290 single reservoir stood out as a consistent source of high burden viruses, with every reservoir that  
291 harbors high burden viruses also harboring substantially more viruses that cluster at the lowest  
292 death burdens (Figure 4a). This was not the case for virus family (Figure 4b) or primary  
293 transmission route (Figure 4c); Coronaviridae and Orthomyxoviridae and a respiratory  
294 transmission route were associated only with high burden zoonotic viruses. In general, the  
295 viruses linked to the lowest death burdens were associated with the lowest transmission capacity.  
296 As a deviation from this trend, Primates—which our models indicate harbor the most  
297 transmissible, but generally less virulent zoonotic viruses—harbored several highly transmissible  
298 viruses with low death burdens (Figure 4a).

299 The highest death burdens were overall associated with zoonotic viruses that are less  
300 virulent but highly transmissible in human populations (Figure 4d). Respiratory pathogens with  
301 capacity for human-to-human transmission have often incurred massive burdens over short  
302 timeframes as a result of rare, but catastrophic spillover events that spark widespread  
303 transmission in humans. Critically, while our dataset included only six viruses with respiratory  
304 droplets as a primary transmission route—SARS-CoV-1, SARS-CoV-2, MERS CoV, Influenza  
305 A, Nipah, and Monkeypox—these viruses accounted for more than 85.9% of the deaths recorded  
306 for the 86 viruses in our death burden analysis, highlighting respiratory transmission as a high-

307 risk zoonotic trait. However, these data were derived from a notably small sample size, as three  
308 of the six respiratory viruses have caused only a single major epidemic. There was also  
309 substantial variation among these respiratory viruses, with the death burdens associated with  
310 SARS-CoV-1 and SARS-CoV-2 differing by more than 2.5 million.

311 Additionally, several outliers demonstrated that capacity for forward transmission in  
312 human populations does not always predict death burden; it is critical to also consider  
313 epidemiological dynamics across and beyond the human-animal interface. Less transmissible  
314 viruses can accumulate large death burdens over many small, but frequent spillovers, particularly  
315 in systems in which humans regularly interact with animal reservoirs. Rabies, Hantaan (HTNV),  
316 and Japanese Encephalitis viruses have been associated with some of the highest death burdens  
317 induced by viral zoonosis despite lacking forward transmission in human populations (Figure  
318 4d). This is likely because these viruses spill over to humans from animal host populations that  
319 live amongst human communities—Rabies burden is largely driven by spillover from endemic  
320 circulation in domestic dogs (28), HTNV spills over from striped field mouse (*Apodemus*  
321 *agrarius*) populations that inhabit agricultural fields (29), and Japanese encephalitis is amplified  
322 via domesticated pigs (30). Outbreaks in these spillover host populations source human  
323 infections that are dead ends for further transmission but add up to large numbers. Emphasizing  
324 the importance of understanding system-specific dynamics, HTNV had a death burden more than  
325 18 times greater than the combined death burden of all ten other rodent-borne hantaviruses in our  
326 dataset, most likely because other rodent reservoirs of hantaviruses tend to overlap less with  
327 human populations (29). Furthermore, zoonotic viruses that have historically been low burden  
328 pathogens can “unexpectedly” cause high death burdens in the case of virus evolution or unique  
329 epidemiological circumstances (31). For example, Ebola virus first emerged in humans in 1976,  
330 causing deadly, but local outbreaks up until late 2013, when suddenly, emergence in a region  
331 with dense and interconnected human populations, coupled with virus adaptation (32), allowed  
332 an Ebola spillover event to spark a transnational epidemic that in just 2 years, caused more than  
333 6.5 times the total number of deaths recorded from 1976-2013 (31, 33). These outliers suggest  
334 that understanding epidemiological dynamics—within wildlife populations and across and  
335 beyond the human-animal interface—in specific systems is a critical component of predicting  
336 death burden and consequently, danger to human health.

## 337 **Discussion**

338 A key insight from our work is that bats harbor the most virulent zoonotic viruses relative to  
339 other mammalian and avian reservoirs (Figure S1 in *SI Figures*). Given that birds represent the  
340 only other flying vertebrates and that flight adaptations are hypothesized to influence viral  
341 virulence in bats (11), we expected avian viruses to similarly be associated with heightened  
342 CFRs in humans. However, we found that only order Chiroptera had an exceptionally high  
343 positive effect size on CFR in humans, while Aves had a neutral nonsignificant effect. It is of  
344 course possible that we observed this association between Chiroptera and high CFRs in part  
345 because low virulence zoonotic viruses have gone undetected in bat reservoirs; however, other  
346 poorly studied reservoirs are not comparably associated with heightened virulence, suggesting  
347 that detection bias cannot explain our results. Like CFR, transmissibility in humans was also  
348 correlated with reservoir traits, but in this case, Primates—the reservoir group most closely  
349 related to humans—sourced the zoonotic viruses with the highest capacities for forward  
350 transmission in human populations. While a combination of both virus and reservoir taxonomy  
351 predicted virulence and transmissibility, death burden did not correlate with any reservoir group



352 and instead, was a function of viral traits. Nevertheless, our data indicated that mechanisms  
353 driving high death burdens are diverse and often contradict trait-based predictions. Several high-  
354 profile zoonotic viruses linked to significantly higher death burdens than we would expect based  
355 on their capacity for forward transmission in the human population (Figure 4d), suggesting that  
356 death burden is highly dependent on both the contact rate at the human-animal interface and  
357 epidemiological dynamics within the human population—factors which are not fully captured by  
358 the broad explanatory variables considered in trait-based analyses.

359 The surprisingly low virulence of avian zoonotic viruses in contrast to bat-borne viruses  
360 may reflect the extreme phylogenetic distance that separates birds from Primates. In our previous  
361 analysis, we found that mammalian reservoir hosts most closely related to humans harbor less  
362 virulent zoonotic viruses relative to more distantly related mammalian hosts such as bats (10).  
363 This positive correlation between reservoir phylogenetic distance from humans and viral  
364 virulence is consistent with trends that have been reported in cross-species pathogen emergences  
365 in other systems (10, 12, 13), and likely reflects maladaptive virulence resulting from  
366 mismatches in host biology, physiology, and ecology. Clearly, while bats are distantly related to  
367 humans, they are still mammals, whereas birds occupy a separate taxonomic class. It is likely  
368 that the positive correlation between phylogenetic distance and virulence collapses at distances  
369 beyond mammals, because viruses are expected to have a limited capacity to replicate in host  
370 environments that are very different from that of their reservoir, leading to ‘non-host resistance’  
371 (34, 35). Phylogenetic distance dropped from all CFR models likely due to a lack of granularity  
372 in our phylogenetic distance data, which described reservoir host cophenetic distance from  
373 Primates on a time-scaled phylogeny (7), producing only six unique distance values across all of  
374 the reservoir groups in our database. Trends across reservoir host groups overall support the  
375 hypothesis that the positive correlation between phylogenetic distance and virulence collapses at  
376 “extreme” distances. Nevertheless, more studies are needed to parse the effect of phylogenetic  
377 distance on virulence trends in animal-to-human spillovers. The time-scaled phylogeny  
378 represents the only available phylogeny that includes both mammals and birds. Future studies  
379 would benefit from developing additional phylogenies of mammalian and avian reservoirs,  
380 which prioritize immunological or physiological traits that may more accurately proxy  
381 virologically relevant differences in host environments.

382 Chiroptera represented an outlier among distantly related reservoirs, with an undeniably  
383 positive effect size on CFR more than triple that recovered for any other mammalian order.  
384 Consistent with the hypothesis that bats represent a ‘special’ viral reservoir (36), the order  
385 Chiroptera does appear to harbor zoonotic viruses that are uniquely virulent upon spillover to  
386 humans, even when considering virulence effects that might be attributed to their phylogenetic  
387 distance from Primates. In bats, flight adaptations have been linked to viral tolerance, which  
388 previous work suggests may select for high growth rate viruses that could manifest as virulent  
389 upon emergence in less tolerant hosts such as humans (14). Notably, bats experience limited  
390 morbidity or mortality from intracellular infections with only a few known exceptions (36–39).  
391 Conversely, while birds harbor several zoonotic viruses that are virulent in humans such as  
392 Highly Pathogenic Avian Influenza (HPAI), West Nile, and Equine Encephalitis viruses, only  
393 some avian species are tolerant of these infections—many avian species experience morbidity  
394 and mortality (40). Bats and birds are expected to experience similar selective pressures from  
395 flight—they have been found to incur comparable energetic costs while flying, despite different  
396 forms and physiologies (15, 41). However, the two taxonomic groups, within disparate vertebrate  
397 classes, may have responded differently to these selective pressures. Specifically, there is a

398 possibility that bats evolved cellular pathways that protect against both aging and  
399 immunopathology, whereas birds evolved pathways that only protect against aging. For example,  
400 bats have been found to host a suite of cellular-level anti-inflammatory adaptations—including  
401 enhanced cellular autophagy and downregulated signaling pathways linked to the induction of  
402 inflammatory antiviral defenses—which may both mitigate cellular damage induced by bat  
403 metabolism and inhibit immunopathology incurred upon viral infection (36, 42–46). On the other  
404 hand, birds may rely primarily on systemic antioxidant responses (47), which mitigate oxidative  
405 stress, but do not interact so tightly with cellular-level processes that impact viral pathology.  
406 Critically, birds appear to be missing anti-inflammatory protein tristetraprolin (TTP) (48), and  
407 immunopathology is often the cause of death in birds that die from viral infections such as HPAI  
408 and West Nile virus (40). Differences between mammalian and avian immune systems may  
409 additionally play a role in their differing infection outcomes. The immune system is broadly  
410 conserved in amniotes, but some avian immunological features diverge from those of bats and  
411 other mammals: notably, birds lack lymph nodes and instead develop B cells in a specialized  
412 lymphoid organ, the bursa of Fabricius; have heterophil in their white blood cells as opposed to  
413 neutrophil; and produce only three classes of immunoglobulin in contrast to the five produced by  
414 mammals (11). Nevertheless, the differing effects of Chiropteran and avian metabolic  
415 adaptations on viral tolerance and viral evolution remain largely uncharacterized and more basic  
416 research in this field is needed (49).

417 We found that both reservoir host and virus taxonomy predict the virulence and  
418 transmissibility of a virus in the secondary human host, consistent with the expectation that a  
419 virus evolves virulence to maximize reproduction in its reservoir population (50). The optimal  
420 balance between virulence and transmission depends on how the reservoir host population  
421 responds to the virus (the ‘host selective pressure’), which is determined by the ecological,  
422 physiological, and biological traits of the reservoir. While we identified “special” reservoirs of  
423 virulent and transmissible zoonotic viruses, we found that the human death burden incurred by  
424 viral zoonoses does not correlate with any one reservoir host order, including bats, and instead, is  
425 a function of viral traits. Our data demonstrate that mechanisms driving high death burdens are  
426 diverse and often contradict trait-based predictions. High death burdens have resulted from rare  
427 spillover events of highly transmissible viruses that spread widely in the human population;  
428 small, but frequent spillovers of the least transmissible viruses; and historically low-burden  
429 pathogens that take off given the right ecological and evolutionary conditions. This suggests that  
430 ultimately, death burden depends on epidemiological circumstances, which should be shaped, not  
431 by reservoir host traits, but by a combination of viral traits and conditions in the animal host  
432 population and across and beyond the human-animal interface. Notably, the pandemic spread of  
433 SARS-CoV-2 can be attributed to its highly effective respiratory transmission between humans,  
434 a trait linked to its identity within Coronaviridae, rather than its bat origins (indeed, CoVs  
435 demonstrate gastrointestinal tropism in bat reservoirs) (51).

436 Over the course of the last decade, a significant amount of funding and research effort has  
437 been dedicated to identifying correlates of zoonotic risk, often with a long-term aspiration of  
438 identifying ways to anticipate and prevent emerging zoonoses in the future (52–54). This  
439 research increasingly prioritizes viral discovery over longitudinal studies of epidemiological  
440 dynamics and targets animal populations such as bats that have been identified as key zoonotic  
441 reservoirs. While our analysis corroborates the hypothesis that bats are a ‘special’ reservoir for  
442 virulent zoonotic viruses, we also demonstrate that viral traits—not bat reservoirs—pose the  
443 greatest danger to human health. We argue that burden, which does not correlate with any animal

444 reservoir and instead appears to be a function of transmission conditions to and within the human  
445 population, more correctly approximates “danger” to human health than does virus virulence.  
446 While reservoir and viral traits can predict zoonotic capacity, virulence, and transmissibility,  
447 death burden is dependent on system-specific epidemiological dynamics, which are shaped by a  
448 combination of viral traits and conditions in the animal host population and across and beyond  
449 the human-animal interface. Thus, understanding and controlling the mechanisms that drive high  
450 death burdens in humans—high rates of human-animal contact and/or epidemiological dynamics  
451 in the human population that allow discrete spillover events to trigger human epidemics—  
452 requires longitudinal surveillance of specific zoonotic or potentially zoonotic viruses in both  
453 animal and human populations. There is a pressing need for more longitudinal studies of  
454 transmission dynamics in human and wildlife populations to better understand and prevent the  
455 epidemiological conditions that cultivate the most dangerous cases of zoonotic viral emergence.

456

## 457 **Materials and Methods**

458 **Constructing the database.** We curated a comprehensive database of mammalian and avian  
459 zoonotic viruses—and the taxonomic orders of the reservoir hosts from which they were  
460 derived—published by Mollentze et al. 2020 (7). Using the information provided in that database  
461 and supplementing with literature searches, we extracted viruses that met a strict definition of  
462 zoonotic, requiring at least one published human infection in which the virus species was  
463 confirmed by PCR, sequencing, or isolation as well as evidence of animal-to-human  
464 directionality in transmission. We excluded six viruses (Table S2 in *SI Data and Results*) that  
465 have only caused human infections in laboratory settings. We additionally did not include viruses  
466 such as HIV (55) and HCoV-299E (56) that have zoonotic origins, but have maintained separate,  
467 genetically distinct human transmission cycles since before 1950 (Table S3 in *SI Data and*  
468 *Results*). We excluded such viruses for several reasons: precise death and case count records are  
469 sparse pre-1950; viruses that have circulated within the human population for centuries or  
470 decades often have unconfirmed or disputed origins; and over long timescales, viral evolution in  
471 the human population is expected to muddle any relationship between zoonotic history and  
472 dynamics in the human population (31). With this strict inclusion criteria, we compiled 87  
473 unique virus species (Table S1 in *SI Data and Results*). Each virus species was associated with  
474 one reservoir host order, with the exception of Rabies virus and Mammalian 1 orthobornavirus,  
475 which are both known to be maintained by two distinct nonhuman animal reservoir orders in  
476 independent transmission cycles (7).

477 For each virus-reservoir association, we collected both human case fatality rate (CFR) as  
478 a proxy for virulence, and the cumulative global death count as a proxy for burden on the human  
479 population. For CFR, we collected two estimates. First, we recorded existing estimates of global  
480 CFRs from the literature, calculating averages when ranges were reported. Second, for each virus  
481 species, we calculated up to three country-specific CFRs from death and case counts in countries  
482 that have reported the largest outbreaks of that virus—when available, using data that spanned  
483 multiple outbreaks and/or years to maximize sample size and accuracy. We expected that global  
484 CFR estimates would be more precise approximations of virulence, while country-specific CFR  
485 reports would allow us to assess and account for potentially confounding effects of regional  
486 differences in health care and overall infrastructure. For our death burden response variable, we  
487 collected the total number of deaths recorded across the world since 1950. In many cases, our  
488 death count began after 1950, either because a zoonosis first emerged in humans after 1950 or

489 reliable death records were only available for a subset of the timeline. To standardize, we added  
490 a variable for the number of years over which death counts were recorded to use as an offset in  
491 our models. Death and case counts were derived, when available, from the Global Infectious  
492 Diseases and Epidemiology Network (GIDEON) (57)—which contains outbreak data from case  
493 reports, government agencies, and published literature records—and supplemented with  
494 literature searches. All variable descriptions are provided in Table S4 in *SI Data and Results*.

495 We additionally ranked each zoonosis' capacity for transmission within human  
496 populations—a correlate of  $R_0$ —on a four-point scale (10). We assigned a human  
497 transmissibility level of “1” to viruses for which forward transmission in human populations  
498 post-spillover had not been recorded; “2” to viruses for which forward transmission in humans  
499 had been recorded but was described as atypical; “3” to viruses for which transmission within  
500 human populations had occurred regularly but was restricted to self-limiting outbreaks; and “4”  
501 to viruses for which endemic human transmission had been reported.

502 Recording death and case data from laboratory-confirmed outbreaks in the literature  
503 required maintaining a strict definition of zoonotic, excluding some viruses that have been  
504 included in previous meta-analyses (3, 7, 19). We compiled excluded viruses that met looser  
505 inclusion criteria—specifically, seven viruses that have only caused human infections in  
506 laboratory settings and 25 viruses that lacked molecular confirmation of infection of humans, but  
507 still had serological evidence of infection in humans—in a supplementary database (Table S2 in  
508 *SI Data and Results*). Viruses included in previous meta-analyses that met neither our loose nor  
509 strict inclusion criteria are outlined in Table S3 in *SI Data and Results*.

510 Drawing from previously published databases (3, 7, 10), we collected seven variables (*SI*  
511 *Data and Results*, Table S7) that we hypothesized might predict observed variation in human  
512 CFR, capacity for transmission within human populations, and death burden. Given published  
513 correlations between phylogenetic distance and virulence in cross-species spillovers (10, 12, 13,  
514 58, 59), we included the reservoir host group cophenetic distance from Primates. We calculated  
515 this distance variable using a composite time-scaled phylogeny of the mean divergence dates for  
516 all reservoir clades, as presented in the TimeTree database (7, 60). In our prior analysis (10),  
517 phylogenetic distance values were derived from a phylogenetic tree of mammalian cytochrome *b*  
518 sequences (3, 61, 62), which captured significantly more variation between host orders. The  
519 time-scaled phylogeny used in this analysis produced only six unique distance values across all  
520 reservoir groups in our database but represented the only available phylogeny that included both  
521 mammals and birds. We considered both reservoir host and virus taxonomy, recording host order  
522 and virus family. However, only ten avian zoonoses were distributed across several avian  
523 reservoir host orders. To test our hypotheses regarding avian zoonoses, we addressed this small  
524 sample size by aggregating avian reservoir orders into a single “Aves” group, while maintaining  
525 separate host orders for the mammalian reservoirs. Given that the number of zoonoses harbored  
526 by a reservoir group appears to correlate with species diversity within that group (7), we  
527 hypothesized that species diversity might influence reservoir effect size on CFR in humans; thus,  
528 we included reservoir species richness, which we derived from the Catalogue of Life using  
529 version 0.9.6 of the taxize library in R (7, 63), taking the sum of values across bird orders for the  
530 Aves reservoir group. If increasing a reservoir group's total number of zoonotic viruses also  
531 increases their number of virulent zoonoses, reservoir species richness might inflate the mean  
532 CFR of zoonotic viruses harbored by species rich reservoir groups—or alternatively, given that  
533 most zoonotic viruses have low CFRs in humans, species richness might instead reduce the mean

534 CFR associated with these reservoirs. Nevertheless, we expected that higher numbers of zoonotic  
535 virus species would inflate the total death burdens associated with species rich reservoir groups.  
536 We defined a “spillover type” variable to account for the zoonotic transmission chain of each  
537 virus, distinguishing between zoonoses that jump into humans directly from the reservoir  
538 population and those that spillover to humans from bridge hosts (10). While the majority of  
539 zoonoses were linked to single zoonotic transmission chains, there were a few exceptions with  
540 both “direct” and “bridged” spillover. For example, zoonotic Influenza A virus and Nipah virus  
541 (64, 65) have spilled over into the human population directly from their avian and bat reservoirs,  
542 respectively, as well as from domestic pig bridge host populations. In such cases, each spillover  
543 type (i.e., transmission chain) was entered separately in the database. We included an additional  
544 binary variable that identified whether viruses were vector-borne, as both theory (23) and  
545 previous meta-analyses (19, 20) have suggested a relationship between vector-borne  
546 transmission and virulence. Finally, as has been done in other similar meta-analyses, we included  
547 virus species publication count to account for any potential publication bias (3, 10, 59).

548 To pair with our country-specific CFR data, we collected an eighth predictor variable—  
549 gross domestic product per capita (GDPPC)—as a proxy for geographical differences in the  
550 quality of health care and epidemiological control measures.

551 We additionally collected, for each virus species, the transmission route that contributes  
552 the majority of human infections, extending data published by Brierley et al. (19). We then  
553 assessed trends in death burden across transmission types, hypothesizing that density-dependent  
554 transmission, as characteristic of transmission via respiratory droplets, would be associated with  
555 the highest death burdens in human populations.

556 **Statistical analysis.** Given the non-normal distribution of our data, expected nonlinear  
557 relationships, and nested data structures within our predictor variables (66), we applied  
558 generalized additive models (GAMs) in the *mgcv* package in R (67) to assess predictors of CFR,  
559 transmissibility, and death burden in human populations. Rather than manually specifying higher  
560 order polynomial functions, GAMs permit the use of smooth functions to capture nonlinear  
561 relationships between response and predictor variables (66, 67). We fit continuous variables (i.e.,  
562 reservoir group species richness and phylogenetic distance from Primates, and virus species  
563 publication count) as smoothed effects, and all binary (i.e., vector-borne status and spillover  
564 type) and categorical (i.e., reservoir order and virus family) variables as random effects. For  
565 variable selection, we ran all possible model combinations, ranked by AIC, and selected the  
566 models with the lowest AIC values.

567 We first asked, *which reservoir host and virus types are associated with elevated CFRs in*  
568 *human populations following spillover?* We constructed GAMs in the beta regression family to  
569 query the predictive capacity of our predictor variables (*SI Data and Results*, Table S7) on CFR  
570 in humans. We compressed our CFR range to the beta distribution interval (0,1) by applying the  
571 recommended data transformation  $y'' = [y'(N - 1) + 1/2]N$ , where  $N$  is the sample size (68,  
572 69). We modeled all 119 country-specific CFR estimates separately to test whether GDPPC  
573 predicts country-level variation in CFR (Table S6c in *SI Data and Results*). To gage whether  
574 variation in GDPPC among virus’ geographic ranges might confound the trends in global CFR  
575 estimates, we then modeled GDPPC and CFR estimates aggregated at the level of the 86 unique  
576 zoonotic transmission chains (Table S6d in *SI Data and Results*). For this second model, we  
577 calculated a composite GDPPC for each aggregated CFR statistic by weighting each country’s  
578 GDPPC by the proportion of cases in the CFR calculation that were recorded in each country and

579 summing the weighted GDPPCs. We then modeled the global CFR estimates, which were not  
580 tied to any specific system. For all CFR analyses, we modeled unique zoonotic transmission  
581 chains—which we defined as unique reservoir orders and spillover type combinations per virus.  
582 As a result, zoonoses with a single reservoir host order and spillover type were modeled as a  
583 single CFR entry, while those with multiple reservoir orders and/or spillover types (e.g.,  
584 Influenza A and Nipah viruses) were modeled as multiple CFR entries. We excluded five viruses  
585 for which only one human case has been recorded (Table S1 in *SI Data and Results*), deciding  
586 that we could not accurately represent a single observation as a CFR. Our final GAM analysis  
587 included 82 unique virus species with a total of 86 unique zoonotic transmission chains (Table  
588 S5a in *SI Data and Results*).

589 Our strict definition of zoonotic status and inclusion criteria reduced our sample size. To  
590 assess whether our observed trends held across a larger sample of zoonotic viruses, we ran an  
591 additional GAM analysis of global CFR estimates that included viruses with only serological  
592 evidence of infection in humans, viruses that have only caused human infections in laboratory  
593 settings, and viruses for which only one human case has been recorded. This supplementary  
594 GAM analysis included 119 unique virus species with a total of 123 unique zoonotic  
595 transmission chains (Table S6b in *SI Data and Results*).

596 We next asked, *which reservoir host and virus types are associated with elevated*  
597 *capacity for transmission within human populations?* We constructed a GAM in the ‘ocat’  
598 (‘ordered categorical data’) family to query the predictive capacity of our predictor variables on  
599 transmissibility, defining the vector of categorical cut points,  $\theta$ , to match our four-point ranking  
600 scale ( $\theta = 1,2,3,4$ ). We again excluded the five viruses for which only one human case has been  
601 recorded (Table S1 in *SI Data and Results*), deciding that we could not accurately determine  
602 between-human transmissibility based on a single observation. Thus, like our CFR analysis, our  
603 transmissibility analysis included 82 unique virus species with a total of 86 unique zoonotic  
604 transmission chains (Table S5b in *SI Data and Results*).

605 Lastly, we asked, *which reservoir host and virus types are associated with high death*  
606 *burdens in human populations?* The death count data demonstrated strong overdispersion  
607 (Figure S11 in *SI Figures*). Thus, we constructed a negative binomial GAM with the scaled  
608 observation period (i.e., number of years over which the death count was recorded) as an offset.  
609 We considered simpler Poisson GAMs, as well as zero-inflated models, but enhanced residual  
610 quantile-quantile (QQ) plots (70) suggested that these distributions fit poorly. Unlike our CFR  
611 analysis, we did not exclude viruses for which only one human case has been recorded.  
612 However, we did exclude a single virus species—Rotavirus A—for which we were unable to  
613 distinguish between deaths caused by zoonotic strains versus deaths caused by endemic human  
614 strains. Thus, our death burden models included 86 zoonotic viruses with a total of 90  
615 transmission chains (Table S5c and S6f in *SI Data and Results*).

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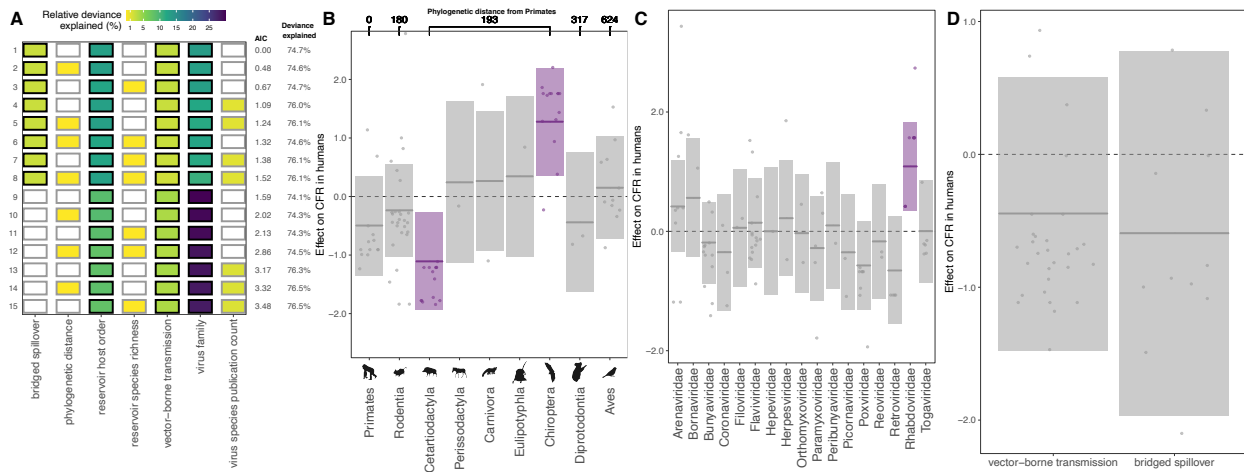
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786 **Figures**



787

788 **Figure 1.** Predictors of global CFR estimates. (A) Top 15 models ranked by AIC. Rows  
 789 represent individual models and columns represent predictor variables. Cells are shaded  
 790 according to the proportion of deviance explained by each predictor. Cells representing predictor  
 791 variables with a p-value significance level of <0.1 are outlined in black. (B-D) Effects present in  
 792 the top model: reservoir host group, virus family, vector-borne transmission, and bridged  
 793 spillover. Lines represent the predicted effect of the x-axis variable when all other variables are  
 794 held at their median value (if numeric) or their mode (if categorical). Shaded regions indicate  
 795 95% CIs by standard error and points represent partial residuals. An effect is shaded in gray if  
 796 the 95% CI crosses zero across the entire range of the predictor variable; in contrast, an effect is  
 797 shaded in purple and considered “significant” if the 95% CI does not cross zero. Full model  
 798 results are outlined in Table S5a in *SI Data and Results*. (B) Reservoir host groups are ordered  
 799 by increasing cophenetic phylogenetic distance from Primates (in millions of years), as indicated  
 800 on the top axis.

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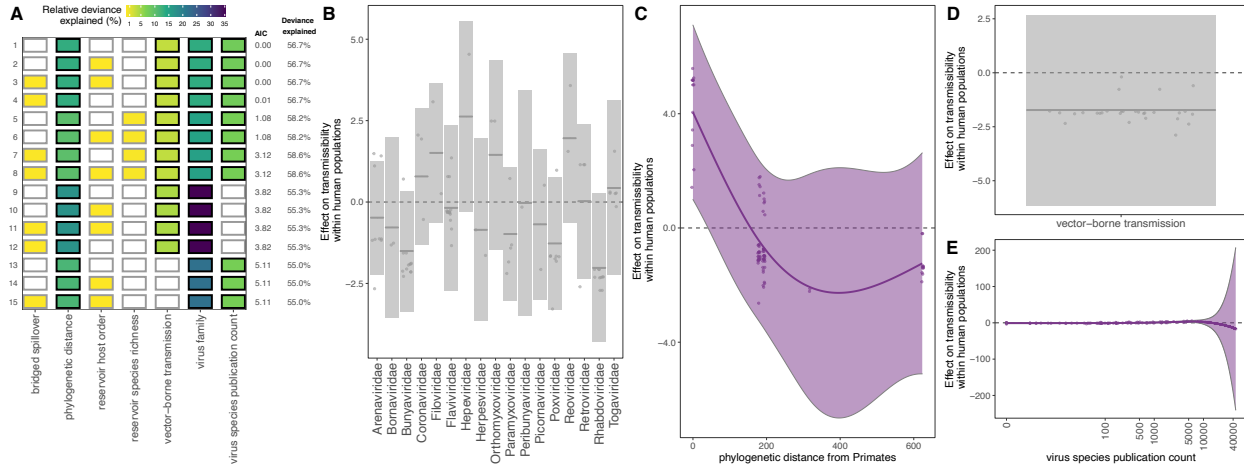
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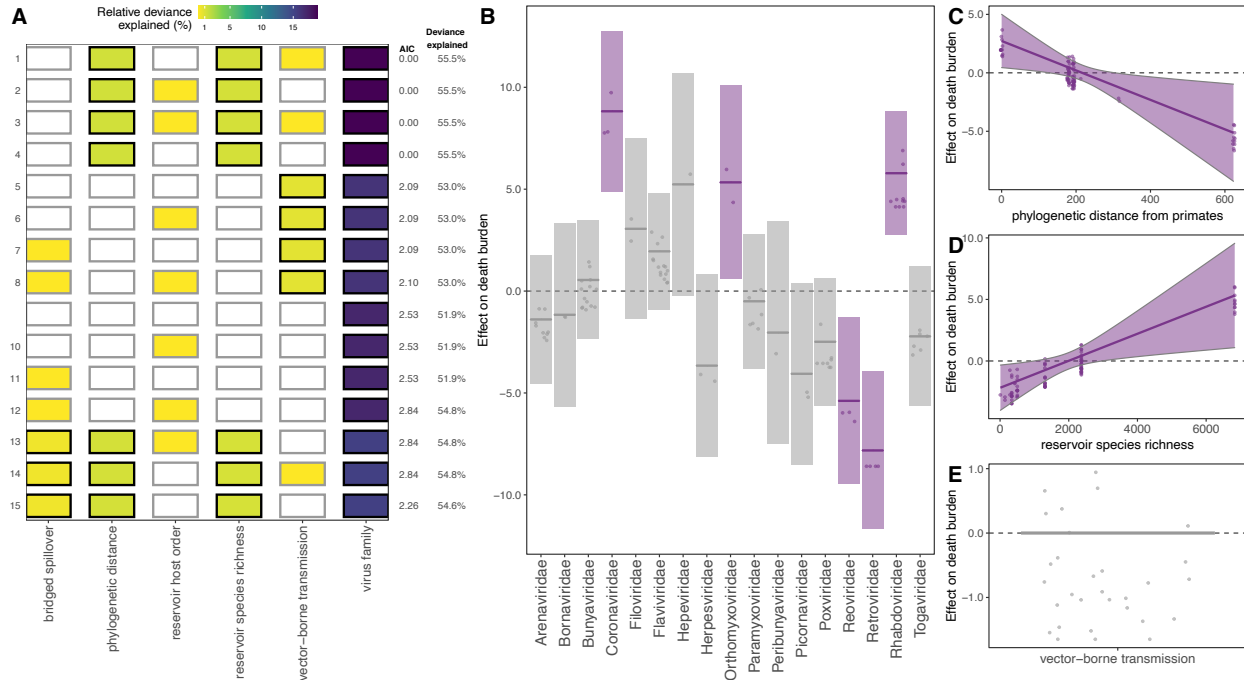


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809 **Figure 2.** Predictors of capacity for forward transmission within the human population following  
 810 zoonotic spillover. (A) Top 15 models ranked by AIC. Rows represent individual models and  
 811 columns represent predictor variables. Cells are shaded according to the proportion of deviance  
 812 explained by each predictor. Cells representing predictor variables with a p-value significance  
 813 level of  $<0.1$  are outlined in black and otherwise outlined in gray. (B-E) Effects present in the top  
 814 model: virus family, reservoir group phylogenetic distance from Primates, vector-borne  
 815 transmission, and virus species publication count. Lines represent the predicted effect of the x-  
 816 axis variable when all other variables are held at their median value (if numeric) or their mode (if  
 817 categorical). Shaded regions indicate 95% CIs by standard error and points represent partial  
 818 residuals. An effect is shaded in gray if the 95% CI crosses zero across the entire range of the  
 819 predictor variable; in contrast, an effect is shaded in purple and considered “significant” if the  
 820 95% CI does not cross zero. Full model results are outlined in Table S5b in *SI Data and Results*.

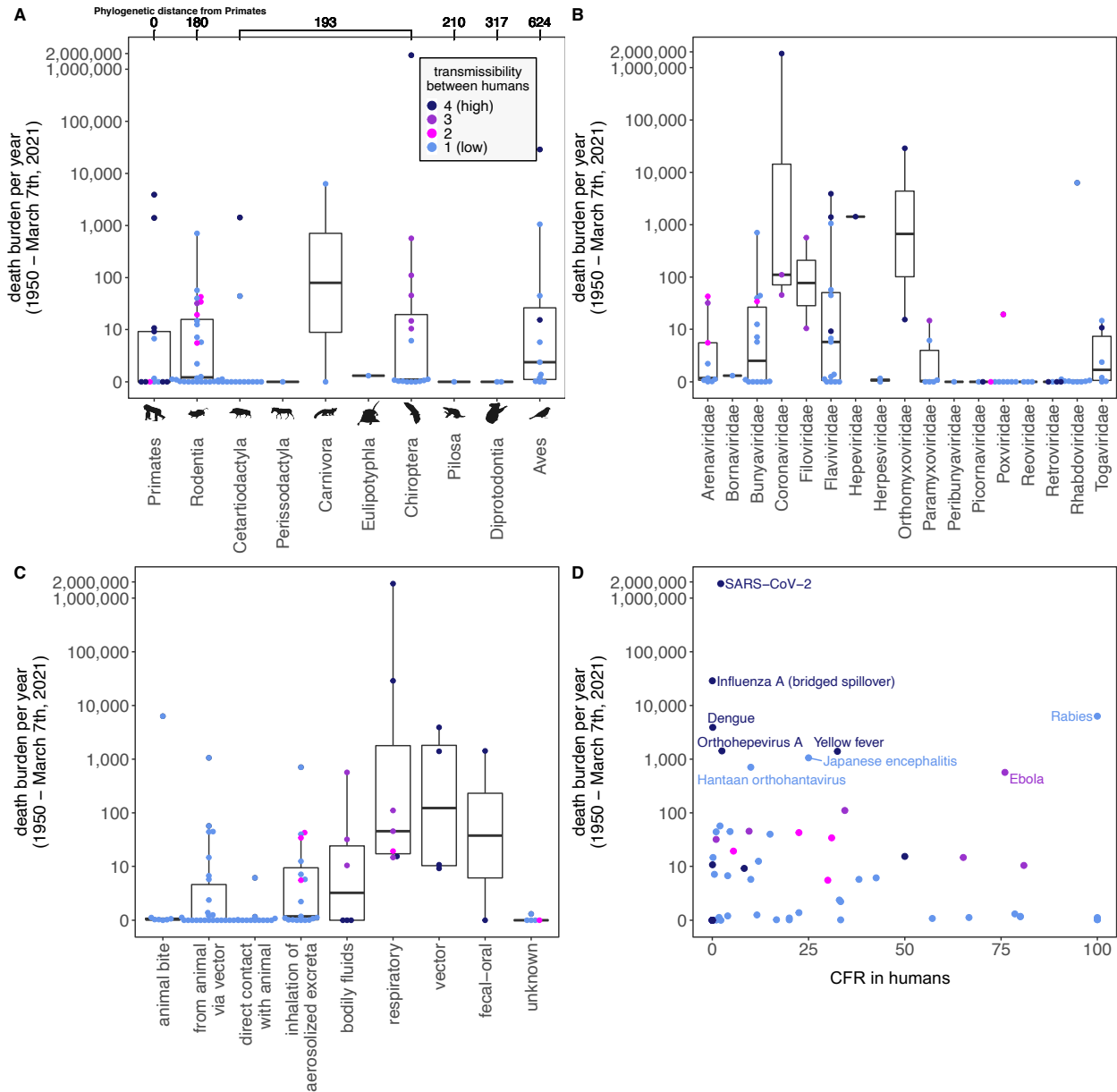
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824 **Figure 3.** Predictors of post-1950 death burden, excluding the virus species publication count  
 825 predictor. See Figure S12 in *SI Figures* for inclusion. (A) Top 15 models ranked by AIC. Rows  
 826 represent individual models and columns represent predictor variables. Cells are shaded  
 827 according to the proportion of deviance explained by each predictor. Cells representing predictor  
 828 variables with a p-value significance level of <0.1 are outlined in black and otherwise outlined in  
 829 gray. (B-D) Effects present in the top model: virus family, reservoir group phylogenetic distance  
 830 from Primates, reservoir group species richness, and vector-borne transmission. Lines represent  
 831 the predicted effect of the x-axis variable when all other variables are held at their median value  
 832 (if numeric) or their mode (if categorical). Shaded regions indicate 95% CIs by standard error  
 833 and points represent partial residuals. An effect is shaded in gray if the 95% CI crosses zero  
 834 across the entire range of the predictor variable; in contrast, an effect is shaded in purple and  
 835 considered “significant” if the 95% CI does not cross zero. Full model results are outlined in  
 836 Table S5c in *SI Data and Results*.



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838 **Figure 4.** Death burden per year (cumulative post-1950 death counts divided by the length of  
 839 reporting time), grouped by (A) reservoir host group, (B) virus family, (C) primary transmission  
 840 route, and (D) CFR in humans. Colors indicate transmissibility between humans, with “1”  
 841 indicating the lowest level of transmission (i.e., no recorded forward transmission in human  
 842 population post-spillover) and “4” indicating the highest level of transmission (i.e., record of  
 843 endemic transmission in human populations post-spillover). (A) Reservoir host groups are  
 844 ordered by increasing cophenetic phylogenetic distance from Primates (in millions of years), as  
 845 indicated on the top axis.

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850 **Supplementary Material**

851 **SI\_Data\_and\_Results.** Databases with variable descriptions and references, and table outputs  
852 for all selected models

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854 **SI\_Figures.** Supplementary figures (Figure S1-12)

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856 **Additional Information**

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858 **Data and materials availability:** All data, data references, code, and materials used in the  
859 analysis are publicly available in the main text, the supplementary materials, or the following  
860 github repository: [https://github.com/sguth1993/zoonotic\\_risk\\_meta\\_analysis](https://github.com/sguth1993/zoonotic_risk_meta_analysis)

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872 **Authors' Contributions**

873 S.G., C.E.B., D.S., and N.M. conceived the study and design. S.G., C.E.B., K.R., and N.M.  
874 collected the data and conducted the analyses. All authors participated in writing the manuscript.

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876 **Competing Interests**

877 The authors declare that we have no competing interests.

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