

1 **Predicting the zoonotic capacity of mammals to transmit SARS-CoV-2**

2

3 Ilya R. Fischhoff<sup>1\*</sup>, Adrian A. Castellanos<sup>1\*</sup>, João P.G.L.M. Rodrigues<sup>2</sup>, Arvind Varsani<sup>3,4</sup>,  
4 Barbara A. Han<sup>1†</sup>

5

6

7 **Affiliations:**

8 <sup>1</sup> Cary Institute of Ecosystem Studies. Box AB Millbrook, NY 12545, USA

9 <sup>2</sup> Department of Structural Biology, Stanford University School of Medicine, Stanford, CA 94305,  
10 USA

11 <sup>3</sup> The Biodesign Center for Fundamental and Applied Microbiomics, Center for Evolution and  
12 Medicine, School of Life Sciences, Arizona State University, Tempe, AZ 85287, USA

13 <sup>4</sup> Structural Biology Research Unit, Department of Integrative Biomedical Sciences, University of  
14 Cape Town, Rondebosch, 7700, Cape Town, South Africa

15

16 \* contributed equally

17 † corresponding author

18

19 **Email addresses:**

20 Ilya Fischhoff: [fischhoff@gmail.com](mailto:fischhoff@gmail.com)

21 Adrian A. Castellanos: [castellanosa@caryinstitute.org](mailto:castellanosa@caryinstitute.org)

22 João P.G.L.M. Rodrigues: [joaor@stanford.edu](mailto:joaor@stanford.edu)

23 Arvind Varsani: [arvind.varsani@asu.edu](mailto:arvind.varsani@asu.edu)

24 Barbara A. Han: [hanb@caryinstitute.org](mailto:hanb@caryinstitute.org)

25

26 **Keywords:** coronavirus; COVID-19; hosts; reservoirs; ecological traits; zoonotic; spillover;  
27 spillback; susceptibility; machine learning; homology modelling; ACE2

28

29 **Abstract**

30 Back and forth transmission of SARS-CoV-2 between humans and animals may lead to wild  
31 reservoirs of virus that can endanger efforts toward long-term control of COVID-19 in people,  
32 and protecting vulnerable animal populations that are particularly susceptible to lethal disease.  
33 Predicting high risk host species is key to targeting field surveillance and lab experiments that  
34 validate host zoonotic potential. A major bottleneck to predicting animal hosts is the small  
35 number of species with available molecular information about the structure of ACE2, a key  
36 cellular receptor required for viral cell entry. We overcome this bottleneck by combining species'  
37 ecological and biological traits with 3D modeling of virus and host cell protein interactions using  
38 machine learning methods. This approach enables predictions about the zoonotic capacity of  
39 SARS-CoV-2 for over 5,000 mammals — an order of magnitude more species than previously  
40 possible. The high accuracy predictions achieved by this approach are strongly corroborated by  
41 *in vivo* empirical studies. We identify numerous common mammal species whose predicted  
42 zoonotic capacity and close proximity to humans may further enhance the risk of spillover and  
43 spillback transmission of SARS-CoV-2. Our results reveal high priority areas of geographic  
44 overlap between global COVID-19 hotspots and potential new mammal hosts of SARS-CoV-2.  
45 With molecular sequence data available for only a small fraction of potential host species,  
46 predictive modeling integrating data across multiple biological scales offers a conceptual  
47 advance that may expand our predictive capacity for zoonotic viruses with similarly unknown  
48 and potentially broad host ranges.  
49

50

## 51 Introduction

52 The ongoing COVID-19 pandemic has surpassed 3.9 million deaths globally as of 25  
53 June 2021 [1,2]. Like previous pandemics in recorded history, COVID-19 originated from the  
54 spillover of a zoonotic pathogen, SARS-CoV-2, a betacoronavirus originating from an unknown  
55 animal host [3–6]. The broad host range of SARS-CoV-2 is due in part to its use of a highly  
56 conserved cell surface receptor to enter host cells, the angiotensin-converting enzyme 2  
57 receptor (ACE2) [7] found in all major vertebrate groups [8].

58

59 The ubiquity of ACE2 coupled with the high prevalence of SARS-CoV-2 in the global  
60 human population explains multiple observed *spillback* infections since the emergence of  
61 SARS-CoV-2 in 2019 (see natural infections listed in Table 1 with references). In spillback  
62 infection, human hosts transmit SARS-CoV-2 virus to cause infection in non-human animals. In  
63 addition to threatening wildlife and domestic animals, repeated spillback infections may lead to  
64 the establishment of new animal hosts from which SARS-CoV-2 can continue to pose a risk of  
65 *secondary spillover* infection to humans through bridge hosts (e.g., [9]) or newly established  
66 enzootic reservoirs. Indeed, this risk has already been realized in Denmark [10] and The  
67 Netherlands, where SARS-CoV-2 spilled back from humans to farmed mink (*Neovison vison*)  
68 with secondary spillover of a SARS-CoV-2 variant from mink back to humans [11]. A major  
69 concern in such secondary spillover events is the appearance of a mutant strain [11,12]  
70 affecting host range [13] or leading to increased transmissibility in humans [14,15] (but see  
71 [16,17]). Preliminary evidence shows that the mink-derived variant exhibits moderately reduced  
72 sensitivity to neutralizing antibodies [10], raising concerns that humans may eventually  
73 experience infections from spillback variants, and that vaccines may become less efficient at  
74 conferring immunity to these variants [18]. Conversely, human-derived variants pose spillback  
75 risks to animals. For example, in contrast to previous infection trials [19], two new human  
76 variants are now confirmed to have overcome the species barrier to infect lab mice (*Mus*  
77 *musculus*) [20].

78

79 Spillback infections from humans to animals are already occurring worldwide. A variety  
80 of pets, domesticated animals, zoo animals, and wildlife have also been documented as new  
81 hosts of SARS-CoV-2 (Table 1). In addition to secondary spillover infections from mink farms,  
82 SARS-CoV-2 has been found for the first time in wild and escaped mink in multiple states in the  
83 United States, with viral sequences identical to SARS-CoV-2 in nearby farmed mink [21–23].  
84 The global scale of human infections and the increasing range of known hosts observed for  
85 SARS-CoV-2 demonstrate that SARS-CoV-2 has the capacity to establish novel enzootic  
86 infection cycles in animals. In response, recent computational studies make predictions about  
87 the susceptibility of particular animal species to SARS-CoV-2 [13,24–32]. These studies  
88 compare known sequences of ACE2 orthologs across species (*sequence-based* studies), or  
89 model the structure of the viral spike protein bound to ACE2 orthologs (*structure-based* studies).  
90 These studies yield a wide range of predictions with varying degrees of agreement with  
91 laboratory animal experiments (Figure 1).

92

93

94 **Table 1.** Species with confirmed suitability for SARS-CoV-2 infection from natural infections or *in vivo*  
 95 experiments. Asterisks reference species with infection status from preprints (not yet peer-reviewed).  
 96 Some species (e.g, dogs) with natural infection studies also have *in vivo* experimental studies.

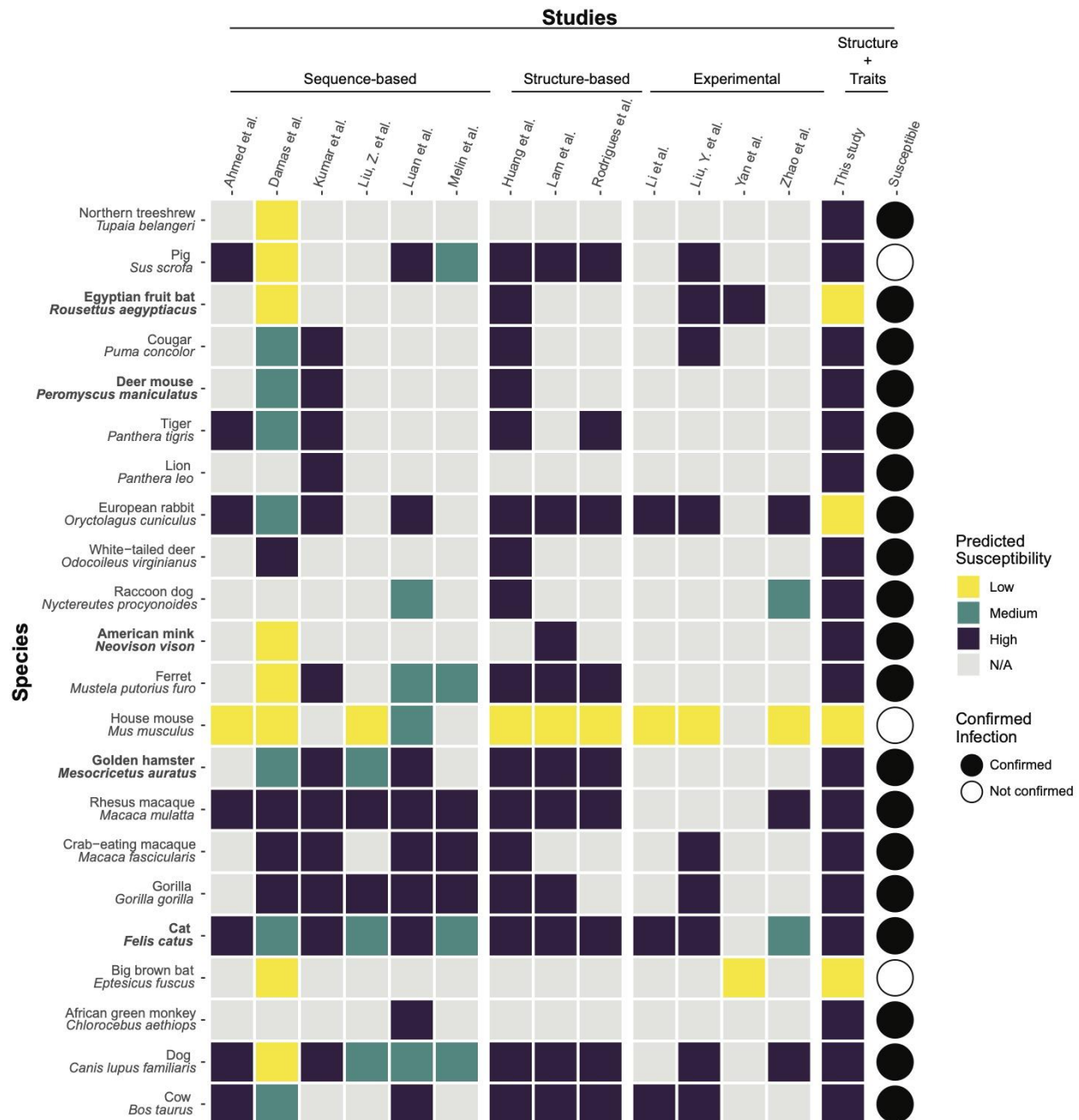
Species	Susceptibility	Study type	Location	References
Cow ( <i>Bos taurus</i> )	Yes	<i>In vivo</i> experiment	Lab	[33]
Dog ( <i>Canis lupus familiaris</i> )	Yes	Natural infection	Multiple countries	[34–38]
African green monkey ( <i>Chlorocebus aethiops</i> )	Yes	<i>In vivo</i> experiment	Lab	[39]
Big brown bat ( <i>Eptesicus fuscus</i> )	No	<i>In vivo</i> experiment	Lab	[40]
Cat ( <i>Felis catus</i> )	Yes	Natural infection	Multiple countries	[35,36,38,41]
Gorilla ( <i>Gorilla gorilla</i> )	Yes	Natural infection	USA, Zoo	[42]
Crab-eating macaque ( <i>Macaca fascicularis</i> )	Yes	<i>In vivo</i> experiment	Lab	[43]
Rhesus macaque ( <i>Macaca mulatta</i> )	Yes	<i>In vivo</i> experiment	Lab	[44]
Golden hamster ( <i>Mesocricetus auratus</i> )	Yes	<i>In vivo</i> experiment	Lab	[45]
House mouse ( <i>Mus musculus</i> )	No	<i>In vivo</i> experiment	Lab	[19] (but see [20])
Ferret ( <i>Mustela putorius furo</i> )	Yes	<i>In vivo</i> experiment	Lab	[37]
American mink ( <i>Neovison vison</i> )	Yes	Natural infection	Multiple countries	[35,36,46]
Raccoon dog ( <i>Nyctereutes procyonoides</i> )	Yes	<i>In vivo</i> experiment	Lab	[47]

European rabbit ( <i>Oryctolagus cuniculus</i> )	Yes	<i>In vivo</i> experiment	Lab	[48]
Lion ( <i>Panthera leo</i> )	Yes	Natural infection	Multiple countries, Zoos	[36,49]
Tiger ( <i>Panthera tigris</i> )	Yes	Natural infection	USA and Sweden, Zoos	[35,36,49,50]
Deer mouse ( <i>Peromyscus maniculatus</i> )*	Yes	<i>In vivo</i> experiment	Lab	[51,52]
Cougar ( <i>Puma concolor</i> )	Yes	Natural infection	South Africa, Zoo	[36]
Egyptian fruit bat ( <i>Rousettus aegyptiacus</i> )	Yes	<i>In vivo</i> experiment	Lab	[53]
Pig ( <i>Sus scrofa</i> )	No	<i>In vivo</i> experiment	Lab	[37,53]
Northern treeshrew ( <i>Tupaia belangeri</i> )	Yes	<i>In vivo</i> experiment	Lab	[54]
Snow leopard ( <i>Uncia uncia</i> )	Yes	Natural infection	USA, Zoo	[55]
Bank vole ( <i>Clethrionomys glareolus</i> )	Yes	<i>In vivo</i> experiment	Lab	[56]
Asian small-clawed otter ( <i>Aonyx cinereus</i> )	Yes	Natural infection	USA, Zoo	[36,57]
White-tailed deer ( <i>Odocoileus virginianus</i> )	Yes	<i>In vivo</i> experiment	Lab	[58]

97

98

99



100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110

**Figure 1.** A heatmap summarizing predicted susceptibility to SARS-CoV-2 for species with confirmed infection from *in vivo* experimental studies or from documented natural infections. Studies that make predictions about species susceptibility are shown on the x-axis, organized by method of prediction (those relying on ACE2 sequences, estimating binding strength using three dimensional structures, or laboratory experiments). Predictions about zoonotic capacity from this study are listed in the second to last column, with high and low categories determined by zoonotic capacity observed in *Felis catus*. Confirmed infections for species along the y-axis are summarized in [59] and are depicted as a series of filled or unfilled circles. Bolded species have been experimentally confirmed to transmit SARS-CoV-2 to naive conspecifics. Species predictions range from warmer colors (yellow: low susceptibility or zoonotic capacity for SARS-CoV-2) to cooler colors (purple: high susceptibility or zoonotic capacity). See

111 Supplementary Methods (<https://doi.org/10.25390/caryinstitute.c.5293339>) for detailed methods  
112 about study categorization.

### 113 Sequence-based studies

114 Sequence-based studies predict host susceptibility based on amino acid sequence  
115 similarity between human (hACE2) and non-human ACE2, and assume that a high degree of  
116 similarity correlates with stronger viral binding, especially at amino acid residues where hACE2  
117 interacts with the SARS-CoV-2 spike glycoprotein. For some species, such as rhesus  
118 macaques [60], these qualitative predictions are borne out by *in vivo* studies (Figure 1), but  
119 predictions from these methods do not consistently match real-world outcomes. For example,  
120 sequence similarity predicted weak viral binding for minks and ferrets, which have all been  
121 confirmed as highly susceptible, with minks capable of onward transmission [11,32,37] (Figure  
122 1). These mismatches to experimental or real-world outcomes may arise in part because protein  
123 three-dimensional structure, the main determinant of protein function, is incompletely  
124 represented by 1D amino acid sequences [61,62]. As such, details about the interaction  
125 between host ACE2 and the viral spike protein are not well captured by sequence-based  
126 studies.

### 127 Structure-based studies

128 Modeling the three-dimensional structure of protein-protein complexes addresses some  
129 of the limitations of sequence-based approaches, and has proven useful to predict how different  
130 ACE2 orthologs bind to the SARS-CoV-2 viral spike protein receptor-binding domain (RBD)  
131 [13,24]. These studies have also identified particular ACE2 amino acid residues essential for a  
132 productive interaction with the viral RBD, thus improving predictive models of susceptibility  
133 through structure-based inference [13]. These studies leverage known structures of the hACE2  
134 receptor bound to the SARS-CoV-2 RBD and use powerful simulation methods to predict how  
135 variation across different ACE2 orthologs affects binding with the viral RBD. While these  
136 approaches successfully predicted strong binding for species that have been infected (e.g.  
137 domestic cat, tiger, dog, and ferret) and weak binding for species in which experimental  
138 infections failed (e.g. chicken, duck [37], mouse [19]), the results are also not consistently  
139 supported by experiments. For instance, while guinea pig ACE2 scored favorably among  
140 susceptible species in one of the studies [13], this ortholog was shown experimentally not to  
141 bind to the SARS-CoV-2 RBD [63].

142  
143 Although structural modeling has produced the most accurate results to date, all  
144 currently available approaches for predicting the host range of SARS-CoV-2 are fundamentally  
145 constrained by the availability and quality of ACE2 sequences across species. ACE2 is  
146 ubiquitous across chordates, likely because of its role in several highly conserved physiological  
147 pathways [64]. Because it is so highly conserved, the vast majority of mammal species (>6,000  
148 species) are likely to have ACE2 receptors, but there are many fewer sequences available from  
149 which to make predictions using existing modeling methods (~300 species). The functional  
150 importance of the ACE2 receptor suggests that it has evolved in association with other intrinsic

151 organismal traits that are more easily observed and for which data are available for many more  
152 species. These suites of correlated organismal traits may provide a robust statistical proxy that  
153 can be leveraged to predict suitable hosts for SARS-CoV-2. Previous trait-based analyses  
154 applied statistical (machine) learning techniques to accurately distinguish the zoonotic capacity  
155 of various organisms [65–67], and predict likely hosts for particular groups of related viruses  
156 [68,69], predictions which have subsequently been validated through independent laboratory  
157 and field investigations (e.g., [70,71]).

158  
159 Here, we combine molecular structural modeling of viral binding with machine learning of  
160 species-level ecological and biological traits to predict species' zoonotic capacity for SARS-  
161 CoV-2 virus across 5,400 mammal species, expanding our predictive capacity by an order of  
162 magnitude (Figure 2). Crucially, this integrated approach enables predictions for the vast  
163 majority of species whose ACE2 sequences are currently unavailable by leveraging information  
164 from viral binding dynamics and biological traits of potential hosts. In our workflow (Figure 2), we  
165 first carry out structural modeling to quantify the binding strength of SARS-CoV-2 RBD for  
166 vertebrate species using published ACE2 amino acid sequences [72]. We then collate species  
167 traits and train a machine learning model to predict the zoonotic capacity for 5,400 mammal  
168 species. Zoonotic capacity (host susceptibility and capacity for onward transmission) was  
169 approximated through a conservative threshold of binding strength applied to our structural  
170 modeling results and reported by *in vivo* studies.

171  
172 COVID-19 is, at this time, primarily a disease affecting humans, thus spillback infection  
173 of SARS-CoV-2 from humans to animals is the most likely mode by which new host species will  
174 become established. We therefore identify a subset of species for which the threat of spillback  
175 infection appears greatest due to geographic overlaps and opportunities for contact with  
176 humans in areas of high SARS-CoV-2 prevalence globally. Our predictions contribute to a  
177 critical interdisciplinary and iterative process between computational modeling, field  
178 surveillance, and laboratory experiments that is necessary for improving zoonotic risk  
179 quantification, and to better inform next steps toward the prevention of enzootic SARS-CoV-2  
180 transmission and spread. We demonstrate our approach using the SARS-CoV-2 sequence that  
181 initially emerged in humans. These methods can be readily expanded to enable host range  
182 predictions for new variants as their hACE2-RBD crystal structures become available.





208 Ambiguous positions in each sequence, artifacts of the sequencing method, were replaced by  
209 Glycine to minimize assumptions about the nature of the amino acid side-chain but still allow for  
210 modeling. For each ortholog, we generated 10 homology models using MODELLER 9.24  
211 [78,79], with restricted optimization (*fastest* schedule) and refinement (*very\_fast* schedule)  
212 settings, and selected a representative model based on the normalized DOPE score. These  
213 representative models were then manually inspected and 27 were removed from further  
214 analysis due to large insertions/deletions or to the presence of too many ambiguous amino  
215 acids at the interface with spike. Each validated model was submitted for refinement to the  
216 HADDOCK web server [80], which ran 50 independent short molecular dynamics simulations in  
217 explicit solvent to optimize the interface between the two proteins. For each one of the animal  
218 species in our study, we assigned an average and standard deviation of the scores of the 10  
219 best refined models, ranked by their HADDOCK score -- a combination of van der Waals,  
220 electrostatics, and desolvation energies. A lower (more negative) HADDOCK score predicts  
221 stronger binding between the two proteins. We hereafter refer to predicted binding strength, or  
222 simply binding strength, to indicate HADDOCK score. The HADDOCK server is freely available,  
223 and we provide code to reproduce analyses or to aid in the application of this modeling  
224 approach to other similar problems (<https://zenodo.org/record/4517509>).

#### 225 Trait data collection and cleaning

226 We gathered ecological and life history trait data from AnAge [81], Amniote Life History  
227 Database [82], and EltonTraits [83], among other databases (Supplementary Table 1; for details  
228 on data processing, see Supplementary Methods with all supplementary data, figures, methods,  
229 and tables available at <https://doi.org/10.25390/caryinstitute.c.5293339>). Using these data, we  
230 also engineered additional traits that have shown importance in predicting host-pathogen  
231 associations in other contexts. For example, as a measure of habitat breadth [84], we computed  
232 for each species the percentage of ecoregions it occupies. To assess the influence of sampling  
233 bias across species, we used the *wosr* R package [85] to count the number of studies returned  
234 in a search in Web of Science for each species' Latin binomial and included this as a proxy for  
235 sampling bias in our model.

236

237 Following the results of initial structural modeling (described above), we observed that  
238 per-residue energy decomposition analysis of HADDOCK scores for 29 species indicated that  
239 all species with strong predicted binding had in common a salt bridge between SARS-CoV-2  
240 K417 and a negatively charged amino acid at position 30 in the ACE2 sequence [13]. Given the  
241 apparent effect of amino acid 30 on overall binding strength, we constructed an additional  
242 feature to denote whether amino acid 30 is negatively charged (and therefore more likely to  
243 support strong binding) and included this feature as an additional trait in our models.

#### 244 Modeling

245

246 *Quantifying a threshold for zoonotic capacity using HADDOCK.* While ACE2 binding is  
247 necessary for viral entry into host cells, it is not sufficient for SARS-CoV-2 transmission. Multiple

248 *in vivo* experiments suggest that not all species that are capable of binding SARS-CoV-2 are  
249 capable of transmitting active infection to other individuals (e.g., cattle, *Bos taurus* [33]; bank  
250 voles, *Myodes glareolus* [56]). Viral replication, and infectious viral shedding that enables  
251 onward transmission, are both required for a species to become a suitable bridge or reservoir  
252 species for SARS-CoV-2. In order to constrain our predictions to species with the greatest  
253 potential to perpetuate onward transmission, we trained our models on a conservative threshold  
254 of binding strength (HADDOCK score = -129). This value is between the scores for two species:  
255 the domestic cat (*Felis catus*), which is currently the species with weakest predicted binding with  
256 confirmed conspecific transmission [86], and the pig (*Sus scrofa*), which shows the strongest  
257 estimated binding for which experimental inoculation failed to cause detectable infection [37].  
258 Binding strength was binarized according to this threshold, above which it is more likely that  
259 both infection and onward transmission will occur following the results of multiple empirical  
260 studies (Table 1). We note that there are species confirmed to be susceptible whose predicted  
261 binding strength is weaker than cats, but conspecific transmission has not been confirmed in  
262 these species. While it is likely that intraspecific transmission will be reported for additional  
263 species as the pandemic continues, the binding strength selected for this analysis represents an  
264 appropriately conservative threshold based on currently available evidence. For additional  
265 modeling details, see Supplementary Methods.

#### 266 Trait-based modeling to predict zoonotic capacity

267 We applied generalized boosted regression [87] to host trait data to predict species'  
268 binding strength to SARS-CoV-2. We applied this approach initially to all of the vertebrate  
269 species for which we estimated HADDOCK scores, but these models did not perform well. This  
270 was likely due to extensive dissimilarities among traits describing different classes of organisms.  
271 For instance, traits that are commonly measured for reptiles are different from those of interest  
272 for birds or amphibians. Moreover, currently available ACE2 sequences are dominated by ray-  
273 finned fishes and mammals.

274  
275 Given that only mammals have so far been confirmed as both susceptible and capable  
276 of onward transmission of SARS-CoV-2, we created a separate set of models to make zoonotic  
277 capacity predictions for mammals only. For this mammal-only dataset, we gathered additional  
278 species-level traits from PanTHERIA [88] and added a series of binary fields for taxonomic  
279 order (based on [89]; Supplementary Table 2). We then applied boosted regression (BRT; gbm  
280 package [90] in R version 4.0.0<sup>[90,91]</sup>) to impute missing trait data for mammal species (e.g., [67];  
281 see Supplementary Methods for details on imputation methods and results).

282  
283 Many of the mammals for which we found the strongest evidence of zoonotic capacity  
284 are domesticated to some degree (pets, farmed or traded animals, lab models) [11,37,53].  
285 Relative to their ancestors or wild conspecifics, domesticated animals often have distinctive  
286 traits [92] that are likely to influence the number of zoonoses found in these species [93]. To  
287 account for trait variation due to domestication in certain species, we modeled mammals in two  
288 ways. First, we incorporated a variable indicating whether the source populations from which  
289 trait data were collected are wild or non-wild (e.g., farmed, pets, laboratory animals; non-wild

290 status confirmed by the Mammal Diversity Database [94]). Trait data collected from both wild  
291 and non-wild individuals were considered to represent non-wild species for the purposes of this  
292 model. In a second approach, we used only the wild species for model training and evaluation.  
293 For both approaches, pre-imputation trait values were used for all non-wild mammals during  
294 model training, evaluation, and prediction.

295  
296 Boosted regression (BRT) is an ensemble machine learning approach that  
297 accommodates non-random patterns of missing data, nonlinear relationships, and interacting  
298 effects among predictors. In a BRT model, a sequence of regression models are fit by recursive  
299 binary splits, with each additional regression modeling those instances that were poorly  
300 accounted for by the previous regression iterations in the tree [87]. We applied grid search to  
301 select optimal hyperparameters, and repeated model fitting 50 times using bootstrapped training  
302 sets of 80% of labeled data. We measured performance by the area under the receiver  
303 operating characteristic curve (AUC) for predictions made on the test dataset (remaining 20%),  
304 corrected by comparing with null models created by target shuffling, which employed similar  
305 bootstrapping (50 times). Detailed methods can be found in Supplementary Methods. We  
306 discuss herein the results of model predictions about zoonotic capacity made by applying this  
307 final model to all mammal species. We also report the mean and variation in predicted  
308 probabilities across all 50 bootstrapped models in Supplementary File 1.

309  
310 To visualize geographic patterns, we mapped the geographic ranges of mammal species  
311 predicted within the 90th percentile of zoonotic capacity for SARS-CoV-2 using International  
312 Union for the Conservation of Nature (IUCN) polygons of species distributions [95]. We subset  
313 to the species found in human-associated habitats (e.g., urban areas, crop lands, heavily  
314 degraded forests; based on IUCN 2020), and also masked their ranges to areas of high human  
315 case counts (using SARS-CoV-2 case data from the COVID-19 Data Repository at Johns  
316 Hopkins University [1]).

317  
318 Additional methods and results of other uninformative model variations are also  
319 described in Supplementary Methods and Supplementary Table 3 (e.g., a model in which  
320 binding strength is modeled as a continuous rather than a threshold measure, a model  
321 predicting the charge at amino acid 30, a model for all vertebrate species)  
322 (<https://doi.org/10.25390/caryinstitute.c.5293339>). We provide code and data files for carrying  
323 out boosted regression tree models  
324 ([https://github.com/HanLabDiseaseEcology/zoonotic\\_capacity](https://github.com/HanLabDiseaseEcology/zoonotic_capacity)). Details about how the species  
325 susceptibility predictions from past studies were standardized into categories (low, medium,  
326 high; Figure 1) are also available in Supplementary Methods.

327  
328

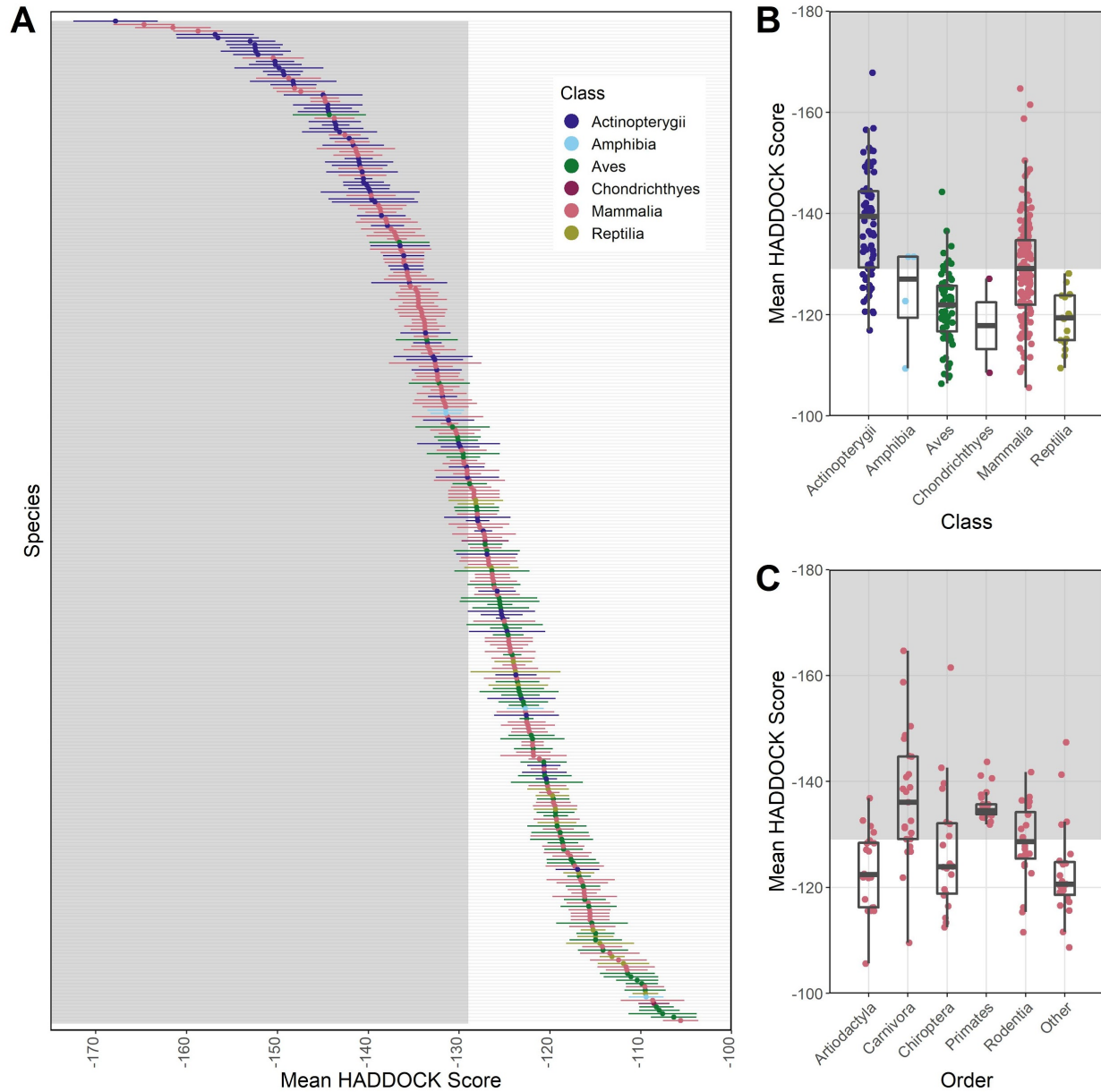
## 329 **Results**

### 330 *ACE2 host protein sequences and alignment*

331 The ACE2 protein sequence alignment of the orthologs from 326 species spans eight  
332 classes and 87 orders (<https://zenodo.org/record/4517509>). The majority of sequences  
333 belonged to the classes Actinopterygii (22.1%), Aves (23.3%), and Mammalia (46.6%).  
334 Sequence length ranged from 344 amino acids to 872 with a median length of 805.

### 335 *Structural modeling of viral binding strength*

336 We predicted binding strength for 299 vertebrates, including 142 mammals. These  
337 binding strength scores represented six classes and 80 orders and ranged between -167.816  
338 and -105.615. Across these six vertebrate classes, the strongest predicted binding between  
339 ACE2 and SARS-CoV-2 (corresponding to the lowest mean HADDOCK scores) were in ray-  
340 finned fishes (Actinopterygii; mean = -137.945) and mammals (Mammalia; mean = -129.193)  
341 (Figure 3A). Four of these six classes included at least one species predicted to have stronger  
342 binding than *Felis catus* (Figure 3B). Among well-represented mammalian orders (those  
343 containing at least 10 species with binding strength predictions), Primates and Carnivora  
344 showed predicted mean binding strengths that were stronger than domestic cats (Figure 3C).  
345



346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356

**Figure 3.** Plots showing results from modeling species' ACE2 interaction with SARS-CoV-2 RBD using HADDOCK to predict binding strength (measured as arbitrary units). HADDOCK scores that predict stronger binding are more negative. The mean and standard deviation of the HADDOCK score for vertebrate species (A) for which ACE2 orthologs are available. Binding strengths vary across vertebrate classes (B) and across the five most speciose mammalian orders (C). The "Other" category contains species across multiple orders for which ACE2 sequences were available, each with fewer than 10 representative species in the order. The shaded regions of all panels represent predicted binding that is as strong or stronger than (more negative values than) the domestic cat (*Felis catus*), which represents our conservative zoonotic capacity threshold based on currently available empirical evidence.

357

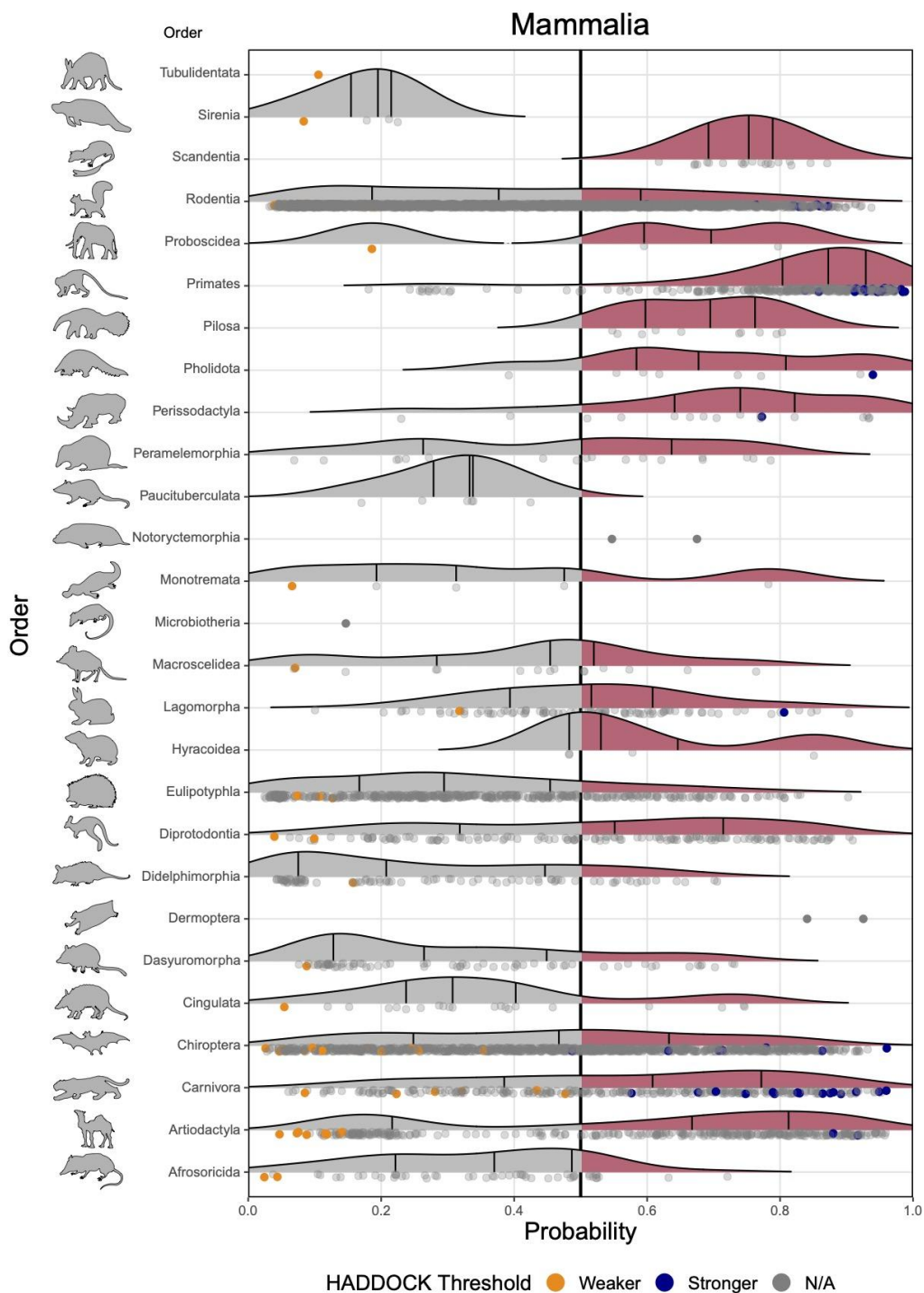
358 *Species predictions of zoonotic capacity from trait-based machine learning models*

359 The best performing model was trained on a mammal-only dataset with trait imputation  
360 and showed corrected test AUC of 0.72 (for results of all other model variations, see  
361 Supplementary Table 3). We used this model to generate predictions of zoonotic capacity  
362 among mammal species. Citation count, as a proxy for study effort, had ~1% relative  
363 importance, suggesting that sampling bias across species had little influence on the model.

364 This zoonotic capacity model identified 540 species (out of 5400 total mammal species)  
365 within the 90th percentile probability (0.826 or higher, compared to a total of 2,401 mammal  
366 species with prediction scores above 0.5; see Supplementary File 1 for predictions on all 5,400  
367 species, <https://doi.org/10.25390/caryinstitute.c.5293339>). The top 10% of species with the  
368 highest predicted probabilities includes representatives from 13 orders. Most primates were  
369 predicted to have high zoonotic capacity and collectively showed stronger viral binding  
370 compared to other mammal groups (Figure 4). Additional orders with numerous species  
371 predicted to have high zoonotic capacity (at least 75% of species above 0.5) include Hyracoidea  
372 (hyraxes), Perissodactyla (odd-toed ungulates), Scandentia (treeshrews), Pilosa (sloths and  
373 anteaters), Pholidota (pangolins), and non-cetacean Artiodactyla (even-toed ungulates) (Figure  
374 4).

375

376



377  
 378  
 379 **Figure 4.** Ridgeline plots showing the distribution of predicted zoonotic capacity across mammals.  
 380 Predicted probabilities for zoonotic capacity across the x-axis range from 0 (likely not susceptible) to 1  
 381 (zoonotic capacity predicted to be the same or greater than *Felis catus*), with the vertical line representing  
 382 0.5. The y-axis depicts all mammalian orders represented by our predictions. Density curves represent  
 383 the distribution of the predictions, with those parts of the curve over 0.5 colored pink and lines  
 384 representing distribution quartiles. The predicted values for each order are shown as points below the



385 density curves. Points that were used to train the model are colored: orange represents species with  
386 weaker predicted binding, blue represents species with stronger predicted binding. Selected family-level  
387 distributions are shown in the Supplemental Figures 5-6  
388 (<https://doi.org/10.25390/caryinstitute.c.5293339>).

389  
390

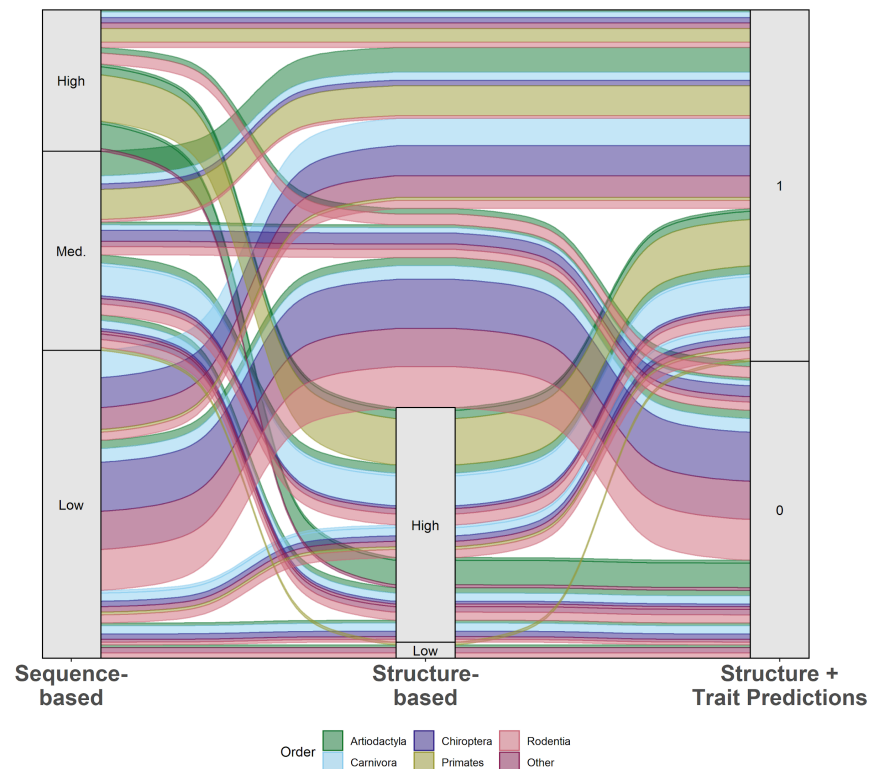
### 391 *Comparison of species predictions*

#### 392 *Comparing species predictions across multiple computational approaches*

393 Our model combined species traits with estimates of viral binding strength to predict  
394 zoonotic capacity, which encompasses both susceptibility to SARS-CoV-2 and the probability of  
395 onward transmission. Zoonotic capacity was defined as a threshold value based on the results  
396 of experimental studies confirming intraspecific transmission among animals, and is therefore  
397 more conservative than thresholds adopted by other studies (e.g., those based only on  
398 estimates of viral binding strength, [30]). In addition, our modeling approach (machine learning)  
399 and prediction targets (zoonotic capacity) differed compared to existing computational  
400 approaches, which applied sequence-based or structure-based analyses constrained by the  
401 small number of published ACE2 sequences. Despite these differences, comparing the species  
402 predictions generated by multiple different approaches can be useful for gauging consensus,  
403 and for comparing how species predictions change from one method to another.

404

405 Across approaches, there was general agreement in the predictions for primates as well  
406 as for a select group of artiodactyls and carnivores (Figure 5). Our model results also agreed  
407 with low susceptibility predictions made by several previous studies using sequence-based  
408 approaches (e.g., in certain bats and rodents). In general, we note that structure-based models  
409 predicted a smaller proportion of species to have low susceptibility compared to sequence-  
410 based studies.



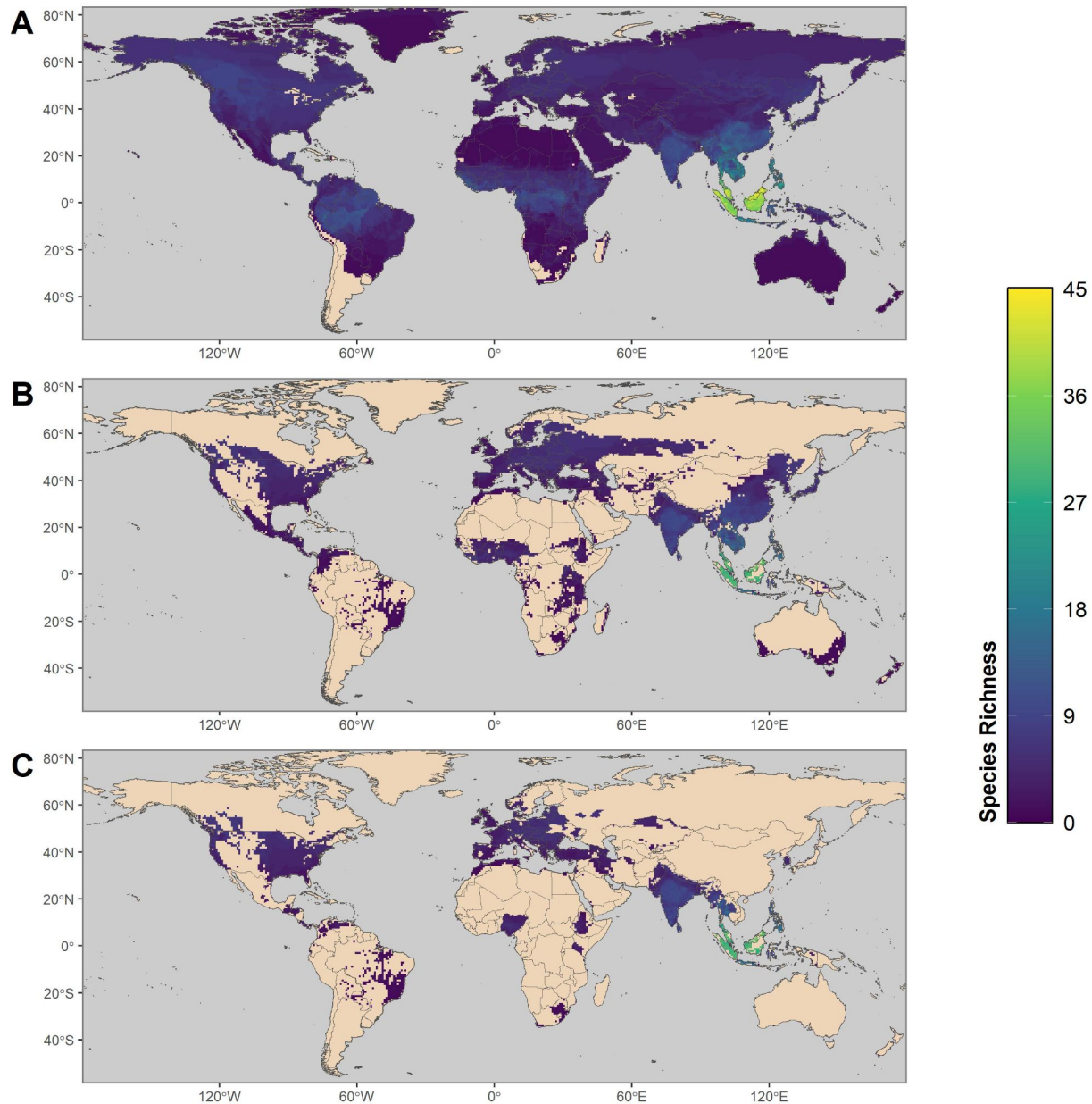
411  
412 **Figure 5.** An alluvial plot comparing predictions of species susceptibility from multiple methods. Existing  
413 studies (listed in Supplementary Methods) are categorized as either sequence-based or structure-based.  
414 Predictions from our zoonotic capacity model result from combining structure-based modeling of viral  
415 binding with organismal traits using machine learning to distinguish species with zoonotic capacity above  
416 (1) or below (0) a conservative threshold value set by domestic cats (*Felis catus*). Colors represent  
417 unique mammalian orders, and the width of colored bands represent the relative number of species with  
418 that combination of predictions across methods. See Supplementary Methods  
419 (<https://doi.org/10.25390/caryinstitute.c.5293339>) for details on how species across multiple studies were  
420 assigned to categories (high, medium, low).  
421

#### 422 *Comparing model predictions to in vivo outcomes*

423 Our model predictions matched the results of several recently published *in vivo* studies  
424 on SARS-CoV-2 infection (Figure 1). For instance, experiments on deer mice (*Peromyscus*  
425 *maniculatus*; [51,52]) and raccoon dogs (*Nyctereutes procyonoides*; [47]) confirmed SARS-CoV-  
426 2 infection and transmission to naive conspecifics. Our model also estimated a high probability  
427 of zoonotic capacity of American mink for SARS-CoV-2 (*Neovison vison*, probability=0.83, 90th  
428 percentile), in which farmed individuals present severe infection from human spillback, and  
429 demonstrate the capacity to transmit to conspecifics as well as to humans [11,46]. Our model  
430 also correctly predicted relatively low zoonotic capacity for big brown bats (*Eptesicus fuscus*;  
431 [40]).

432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443

There were notable differences between our model results and the outcomes of some experimental studies. For instance, our model estimated a moderately high probability of zoonotic capacity for pigs (*Sus scrofa*, probability = 0.72, ~80th percentile). Similarly, some computational and cell-based studies have also predicted strong viral binding in this species [26,96], but *in vivo* studies report no detectable infection or onward transmission of SARS-CoV-2 [37,53]. Similarly for cattle (*Bos taurus*), our model estimated a moderately high probability for zoonotic capacity (0.72, ~80th percentile), and in a live animal experiment, cattle were confirmed to be susceptible to infection but no onward transmission was observed to virus-naive conspecifics [33].



444  
445  
446  
447  
448  
449  
450  
451  
452  
453

**Figure 6:** Maps showing the global distribution of species with predicted capacity to transmit SARS-CoV-2. (A) depicts global species richness of the top 10 percent of model-predicted zoonotic capacity. Geographic ranges of this subset of species were filtered to those associated with human-dominated or human-altered habitats (B), and further filtered to show the subset of species that overlaps with areas of high human SARS-CoV-2 positive case counts (over 100,000 cumulative cases as of 17 May 2021) (C). For a full list of model-predicted zoonotic capacity of species by country, see Supplementary File 2 (<https://doi.org/10.25390/caryinstitute.c.5293339>).

## 454 Discussion

455 We combined structure-based models of viral binding with species-level data on  
456 biological and ecological traits to make predictions about the capacity of animal species to  
457 become zoonotic hosts of SARS-CoV-2 (*zoonotic capacity*). This combined modeling approach  
458 predicted zoonotic capacity with 72% accuracy, extending our predictive capacity beyond the  
459 limited number of species for which ACE2 sequences are currently available. We identified  
460 numerous mammal species whose predicted zoonotic capacity meets or exceeds the viral  
461 susceptibility and transmissibility observed in experimental infections with SARS-CoV-2. In  
462 addition to wide agreement with *in vivo* study results produced to date (Table 1), these model  
463 predictions corroborate the predictions of previous studies generated using the limited number  
464 of available ACE2 sequences (Figure 1). Below we discuss predictions of zoonotic capacity for  
465 a number of ecologically and epidemiologically relevant categories of mammalian hosts.

466  
467 Captive, farmed, or domesticated species. Given that the type and frequency of contact with  
468 humans fundamentally underlies transmission risk, it is notable that our model predicted high  
469 zoonotic capacity for multiple captive species that have also been confirmed as susceptible to  
470 SARS-CoV-2 via experiments or natural infections. These include numerous carnivore species,  
471 such as large cats from multiple zoos and pet dogs and cats. Our model also predicted high  
472 SARS-CoV-2 zoonotic capacity for many farmed, domesticated, and live traded species. The  
473 water buffalo (*Bubalus bubalis*), widely bred for dairy production and farming, had the highest  
474 probability of zoonotic capacity among livestock (0.91). Model predictions in the 90th percentile  
475 also included American mink (*Neovison vison*), red fox (*Vulpes vulpes*), sika deer (*Cervus*  
476 *nippon*), white-lipped peccary (*Tayassu pecari*), nilgai (*Boselaphus tragocamelus*), and raccoon  
477 dogs (*Nyctereutes procyonoides*), all of which are farmed, with the latter two considered  
478 invasive species in some areas [97,98]. In addition to the risks of secondary spillover to humans  
479 and the potential for large economic losses from culling infected animals [99], the escape of  
480 farmed individuals into wild populations has implications for the spread and enzootic  
481 establishment of SARS-CoV-2 [21]. These findings also have implications for vaccination  
482 strategies, for instance, prioritizing people in regular contact with potential bridge species (e.g.,  
483 veterinarians, abattoir-workers, farmers, etc).

484  
485 Live traded or hunted wildlife species. The majority of the legally traded live mammals are  
486 primates and carnivores [100], and model predictions included several species from these  
487 groups. Our model predicted high zoonotic capacity in 20 out of 21 species in the primate genus  
488 *Macaca*, which comprise the majority of all live-traded primates. Several live-traded carnivores  
489 and pangolins were also assigned high zoonotic capacity, including the Asiatic black bear  
490 (*Ursus thibetanus*), grey wolf (*Canis lupus*), and jaguar (*Panthera onca*), the Philippine pangolin  
491 (*Manis culionensis*) and Sunda pangolin (*M. javanica*). Pangolins are notable because one of  
492 the betacoronaviruses with the highest sequence similarity to SARS-CoV-2 was isolated from  
493 Sunda pangolins [101,102]. Pangolin burrows are also known to be occupied by multiple other  
494 animal species, including numerous bats [103].

495

496 Commonly hunted species in the top 10% of predictions include duiker (*Cephalophus*  
497 *zebra*, West Africa), warty pig (*Sus celebes*, Southeast Asia), and two species of deer  
498 (*Odocoileus hemionus* and *O. virginianus*) that are widespread across the Americas. The white-  
499 tailed deer (*O. virginianus*) was recently confirmed to be capable of transmitting SARS-CoV-2 to  
500 conspecifics via indirect contact (aerosolized virus particles) [58].

501  
502 Bats. Similarly, bats are of special interest because of the high diversity of betacoronaviruses  
503 found in *Rhinolophus spp.* and other bat species [104–107]. Our model identified 35 bat species  
504 within the 90th percentile of zoonotic capacity for SARS-CoV-2. Within the genus *Rhinolophus*,  
505 our model identified the large rufous horseshoe bat (*Rhinolophus rufus*), a known natural host  
506 for bat betacoronaviruses [104] and a congener to three other horseshoe bats harboring  
507 betacoronaviruses with high nucleotide sequence similarity to SARS-CoV-2 (~92-96%)  
508 [6,108,109]. For these three species, our model assigned a range of probabilities for SARS-  
509 CoV-2 zoonotic capacity (*Rhinolophus affinis* (0.58), *R. malayanus* (0.70), and *R. shameli*  
510 (0.71)) and also predicted relatively high probabilities for two congeners, *Rhinolophus*  
511 *acuminatus* (0.84) and *R. macrotis* (0.70). These predictions are in agreement with recent  
512 experiments demonstrating efficient viral binding of SARS-CoV-2 RBD for *R. macrotis* [110] and  
513 confirmation of SARS-CoV-2-neutralizing antibodies in field-caught *R. acuminatus* harboring a  
514 closely related betacoronavirus [111].

515  
516 Our model also identified 17 species in the genus *Pteropus* (flying foxes) with high  
517 probabilities of zoonotic capacity for SARS-CoV-2. Some of these species are confirmed  
518 reservoirs of other zoonotic viruses in Southeast Asia (e.g., henipaviruses in *P. lylei*, *P.*  
519 *vampyrus*, *P. conspicillatus*, and *P. alecto*). While contact patterns between bats and humans  
520 may be somewhat less direct compared with captive or farmed species, annual outbreaks  
521 attributed to viral spillover transmission from bats illustrate a persistent epizootic risk to humans  
522 [112–114] and confirm that gaps in systematic surveillance of zoonotic viruses, including  
523 betacoronaviruses, remain an urgent priority (e.g., [115]).

524  
525 Rodents. Our model identified 76 rodent species with high zoonotic capacity for SARS-CoV-2,  
526 some of which thrive in human-altered settings. Among these, the deer mouse (*Peromyscus*  
527 *maniculatus*) and the white-footed mouse (*P. leucopus*) showed high probabilities. These are  
528 among the most well-studied mammals in North America, in part due to their status as zoonotic  
529 reservoirs for multiple zoonotic pathogens and parasites [116–118]. Experimental infection, viral  
530 shedding, and sustained intraspecific transmission of SARS-CoV-2 were recently confirmed for  
531 *P. maniculatus* [51,52], but similar studies have not been conducted for *P. leucopus*, which is  
532 widely distributed across the eastern United States and Mexico.

533  
534 Our model predicted low zoonotic capacity for *Mus musculus* (0.11), corresponding with  
535 *in vivo* experiments suggesting this species is not susceptible to infection by the initial human  
536 variant of SARS-CoV-2[19], although notably, more recent experiments have confirmed the  
537 susceptibility of *M. musculus* to two newer human-derived variants [20]. Also in the top 10%  
538 were two rodent species considered to be human commensals whose geographic ranges are

539 expanding due to human activities: *Rattus argentiventer* (0.84) and *R. tiomanicus* (0.79)  
540 (Supplementary File 1) [119–121]. Additional common rodent species with relatively high  
541 probabilities of zoonotic capacity include domesticated guinea pigs (*Cavia porcellus*), gerbils  
542 (*Gerbillus gerbillus*, *Meriones tristrami*), and several common mouse species (*Apodemus*  
543 *peninsulae*, *A. flavicollis*, and *A. sylvaticus*), all of which are known reservoirs for other zoonotic  
544 diseases [122–124]. It is notable that many of these rodent species are regularly preyed upon  
545 by carnivore species, such as the red fox (*Vulpes vulpes*) or domestic cats (*Felis catus*) who  
546 themselves were predicted to have high zoonotic capacity for SARS-CoV-2 by our model.

547  
548 Species with large geographic ranges. With sufficient opportunity for infectious contact, the risk  
549 of zoonotic spillback transmission increases with SARS-CoV-2 prevalence in human  
550 populations. Among species with high model-predicted zoonotic capacity, there were several  
551 relatively common species with very large geographic ranges or synanthropic tendencies that  
552 overlap with global hotspots of COVID-19 in people (Figure 6, Supplementary File 2). Notable  
553 species that are widely distributed across much of the northern hemisphere include the red fox  
554 (*Vulpes vulpes*, ~50 countries), the European polecat (*Mustela putorius*), the raccoon dog  
555 (*Nyctereutes procyonoides*), stoat (*Mustela erminea*) and wolf (*Canis lupus*). White-tailed deer  
556 (*Odocoileus virginianus*) are among the most geographically widespread species across Latin  
557 American countries with high SARS-CoV-2 prevalence. Globally, South and Southeast Asia had  
558 the highest diversity of mammal species with high predicted zoonotic capacity for SARS-CoV-2  
559 (~90 species). Notable examples in this region include both rodents and bats. For example,  
560 Finlayson’s squirrel (*Callosciurus finlaysonii*) is native to Mainland Southeast Asia, but  
561 introductions via the pet trade in Europe have led to invasive populations in multiple countries  
562 [125]. Hunting has been documented for numerous bat species with geographic ranges across  
563 Southeast Asia (e.g., *Cheiromeles torquatus*, *Cynopterus brachyotis*, *Rousettus*  
564 *amplexicaudatus*, *Macroglossus minimus*) [126,127], and there were multiple additional bat  
565 species in the 90th percentile from Asia and Africa where bats are subject to hunting pressure  
566 and from which other betacoronaviruses have been identified [107,128]. There were also  
567 several wide-ranging species whose contact with humans are limited to specialized settings. For  
568 instance, biologists and wildlife managers handle live individuals for research purposes,  
569 including grizzly bear (*Ursus arctos*), polar bear (*Ursus maritimus*), and wolf (*Canis lupus*), all of  
570 which are in the 89th percentile or above for predicted zoonotic capacity to SARS-CoV-2.

571  
572 Other high priority mammal species. Species with more equivocal predictions about zoonotic  
573 capacity that are in frequent contact with humans warrant further investigation. For instance,  
574 while species such as horses (*Equus caballus*), goats (*Capra hircus*), and guinea pigs (*Cavia*  
575 *porcellus*) are not in the top 10% of predicted zoonotic capacity, due to the nature of their  
576 contact with humans they may experience greater risks of spillback infection, or pose a greater  
577 risk to humans for secondary spillover infection compared to many wild species. Conversely,  
578 while certain endangered or nearly extinct species are predicted to have relatively high zoonotic  
579 capacity, they may have fewer opportunities for human contact. For species of conservation  
580 concern, spillback transmission of SARS-CoV-2 from humans presents an important source of  
581 risk [28,129], particularly for populations that are under active management, including *ex situ*

582 management such as captive breeding. These species include the scimitar-horned oryx (*Oryx*  
583 *dammah*), addax (*Addax nasomaculatus*), some Antarctic fauna, and mountain gorillas (*Gorilla*  
584 *beringei*) in which SARS-CoV-2 spillback infection may occur through close-proximity eco-  
585 tourism activities [130,131]. Indeed, spillback transmission of SARS-CoV-2 has already been  
586 confirmed in a closely related species, the Western lowland gorilla (*Gorilla gorilla*) in captivity  
587 [132], leading to the vaccination of bonobos and orangutans with an experimental COVID-19  
588 vaccine [133]. These species may benefit from focused risk mitigation efforts, such as those  
589 enacted recently to protect endangered black-footed ferrets (*Mustela nigripes*) from potential  
590 SARS-CoV-2 spillback [134].

591

592 All fifteen species of *Tupaia* treeshrews were predicted by our model to have medium to  
593 high probability (ranging from 0.62 to 0.87). One species, *T. belangeri*, has been explored as a  
594 potential lab model for several human infectious diseases including SARS-CoV-2 [135] but  
595 relative to other treeshrews, our model assigned only medium probability for SARS-CoV-2  
596 zoonotic capacity in this species (0.67). This result matches lab studies reporting asymptomatic  
597 infection and low viral shedding in *T. belangeri* [54]. In contrast, the common treeshrew (*T. glis*)  
598 was in the 94th percentile of zoonotic capacity (0.87 probability). These two species are  
599 sympatric in parts of their range, exist in close proximity to humans, and also overlap  
600 geographically with COVID-19 hotspots in Southeast Asia, suggesting the possibility of spillover  
601 transmission among congeners if spillback transmission occurs from humans to these species.

602

603 Strengthening predictive capacity for zoonoses. While there was wide agreement between our  
604 model predictions and empirical studies, examining biases and mismatches between  
605 experimental results and model-generated predictions will focus research attention on  
606 characterizing what factors underlie the disconnects between predicted and observed zoonotic  
607 capacity. For instance, this study along with multiple other computational and experimental  
608 studies predicted that pigs (*Sus scrofa*) would be susceptible to SARS-CoV-2 (Figure 1), but this  
609 prediction has not been supported by results from whole animal inoculations [37,53].

610

611 Disconnects between real-world observations, *in vivo* experimental results, and *in silico*  
612 predictions of zoonotic capacity may arise because host susceptibility and transmission capacity  
613 are necessary but not sufficient for zoonotic risk to be realized in natural settings. These  
614 processes are embedded in a broader ecological context that impacts host susceptibility, intra-  
615 host infection dynamics (latency, recrudescence, tolerance), and viral persistence that  
616 collectively determine where and when spillover will occur [136–139]. These processes also  
617 depend strongly on the cellular environments in which cell entry and viral replication take place  
618 (e.g., the presence of key proteases, [7]), and on host immunogenicity [139], factors which are  
619 themselves influenced by the environment [140]. Insofar as data limitations preclude perfect  
620 computational predictions of zoonotic capacity (e.g., limited ACE2 sequences, crystal structures,  
621 or species trait data), laboratory experiments are also limited in assessing true zoonotic  
622 capacity. For SARS-CoV-2 and other host-pathogen systems, animals that are readily infected  
623 in the lab appear to be less susceptible in non-lab settings (ferrets in the lab vs. mixed results in  
624 ferrets as pets [36,53,141]; rabbits in the lab vs. rabbits as pets [48,142]. Moreover, wildlife



625 hosts confirmed to shed multiple zoonotic viruses in natural settings (e.g., bats, [143]) can be  
626 much less tractable for whole-animal laboratory investigations (for instance, requiring high  
627 biosecurity containment and very limited sample sizes in unnatural settings). While laboratory  
628 experiments are critical for understanding mechanisms of pathogenesis and disease, without  
629 field surveillance and population-level studies they offer imperfect reflections of zoonotic  
630 capacity in the natural world.

631  
632 These examples illustrate that there is no single methodology sufficient to understand  
633 and predict zoonotic transmission, for SARS-CoV-2 or any zoonotic pathogen. They also  
634 demonstrate the need for improved coordination among theoretical and statistical models, lab  
635 work, and field work to improve zoonotic predictive capacity [144], and to create new linkages to  
636 underutilized data sources such as natural history collections, which are well-positioned to  
637 augment basic knowledge gaps about the spatial and temporal extents of animal hosts and their  
638 pathogens [145,146]. Integration of multiple methodologies and data streams across biological  
639 scales offers avenues to more efficient iteration between computational predictions, laboratory  
640 experiments, and targeted animal surveillance that will better link transmission mechanisms to  
641 the broader conditions underpinning zoonotic disease emergence in nature.

642

643

#### 644 **Acknowledgments**

645 We are grateful for discussions with Drs. Alexandre Bonvin, Dennis Bente, Susan  
646 Hafenstein, Kathryn Hanley, Hyunwook Lee, Colin Parrish, and John Paul Schmidt about  
647 various components of this project. This work was supported by the NSF EEID program (DEB  
648 1717282), DARPA PREEMPT program (D18AC00031), CREATE-NEO, a member of the NIH  
649 NIAID CREID program (1U01 AI151807-01), and the NVIDIA Corporation GPU grant program  
650 (BAH); by the NSF Polar program (OPP 1935870, 1947040) (AV); and by NIH NIGMS  
651 (R35GM122543) (JPGLMR).

652

653

#### 654 **Competing interests**

655 The authors declare no competing interests.

656

657  
658  
659

## References

- 660 1. Dong E, Du H, Gardner L. 2020 An interactive web-based dashboard to track COVID-19 in  
661 real time. *Lancet Infect. Dis.* **20**, 533–534. (doi:10.1016/S1473-3099(20)30120-1)
- 662 2. WHO. 2021 WHO coronavirus disease (COVID-19) dashboard.
- 663 3. Keele BF *et al.* 2006 Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science*  
664 **313**, 523–526. (doi:10.1126/science.1126531)
- 665 4. Gage KL, Kosoy MY. 2005 Natural history of plague: perspectives from more than a  
666 century of research. *Annu. Rev. Entomol.* **50**, 505–528.  
667 (doi:10.1146/annurev.ento.50.071803.130337)
- 668 5. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. 2005  
669 Characterization of the 1918 influenza virus polymerase genes. *Nature* **437**, 889.  
670 (doi:10.1038/nature04230)
- 671 6. Zhou P *et al.* 2020 A pneumonia outbreak associated with a new coronavirus of probable  
672 bat origin. *Nature* **579**, 270–273. (doi:10.1038/s41586-020-2012-7)
- 673 7. Letko M, Marzi A, Munster V. 2020 Functional assessment of cell entry and receptor usage  
674 for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* **5**, 562–569.  
675 (doi:10.1038/s41564-020-0688-y)
- 676 8. Chou C-F *et al.* 2006 ACE2 orthologues in non-mammalian vertebrates (Danio, Gallus,  
677 Fugu, Tetraodon and Xenopus). *Gene* **377**, 46–55. (doi:10.1016/j.gene.2006.03.010)
- 678 9. Guth S, Visher E, Boots M, Brook CE. 2019 Host phylogenetic distance drives trends in  
679 virus virulence and transmissibility across the animal-human interface. *Philos. Trans. R.*  
680 *Soc. Lond. B Biol. Sci.* **374**, 20190296. (doi:10.1098/rstb.2019.0296)
- 681 10. WHO. 2020 SARS-CoV-2 mink-associated variant strain – Denmark.
- 682 11. Oude Munnink BB *et al.* 2020 Transmission of SARS-CoV-2 on mink farms between  
683 humans and mink and back to humans. *Science* (doi:10.1126/science.abe5901)
- 684 12. Garry RF. 2021 Mutations arising in SARS-CoV-2 spike on sustained human-to-human  
685 transmission and human-to-animal passage. *Virological*. See  
686 [https://virological.org/t/mutations-arising-in-sars-cov-2-spike-on-sustained-human-to-](https://virological.org/t/mutations-arising-in-sars-cov-2-spike-on-sustained-human-to-human-transmission-and-human-to-animal-passage/578)  
687 [human-transmission-and-human-to-animal-passage/578](https://virological.org/t/mutations-arising-in-sars-cov-2-spike-on-sustained-human-to-human-transmission-and-human-to-animal-passage/578) (accessed on 28 January 2021).
- 688 13. Rodrigues JPGLM, Barrera-Vilarmau S, M C Teixeira J, Sorokina M, Seckel E, Kastritis PL,  
689 Levitt M. 2020 Insights on cross-species transmission of SARS-CoV-2 from structural  
690 modeling. *PLoS Comput. Biol.* **16**, e1008449. (doi:10.1371/journal.pcbi.1008449)
- 691 14. Davies NG *et al.* 2020 Estimated transmissibility and severity of novel SARS-CoV-2 Variant  
692 of Concern 202012/01 in England. *medRxiv*, 2020.12.24.20248822.  
693 (doi:10.1101/2020.12.24.20248822)

- 694 15. Volz E *et al.* 2021 Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from  
695 linking epidemiological and genetic data. *medRxiv* , 2020.12.30.20249034.  
696 (doi:10.1101/2020.12.30.20249034)
- 697 16. Rambaut A *et al.* 2020 Preliminary genomic characterisation of an emergent SARS-CoV-2  
698 lineage in the UK defined by a novel set of spike mutations. *Virological*. See  
699 [https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-](https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563)  
700 [lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563](https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563) (accessed on 28 January  
701 2021).
- 702 17. Tegally H *et al.* 2020 Emergence and rapid spread of a new severe acute respiratory  
703 syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in  
704 South Africa. *medRxiv* , 2020.12.21.20248640. (doi:10.1101/2020.12.21.20248640)
- 705 18. Van Egeren D *et al.* 2021 Risk of rapid evolutionary escape from biomedical interventions  
706 targeting SARS-CoV-2 spike protein. *PLoS One* **16**, e0250780.  
707 (doi:10.1371/journal.pone.0250780)
- 708 19. Bao L *et al.* 2020 The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature*  
709 **583**, 830–833. (doi:10.1038/s41586-020-2312-y)
- 710 20. Montagutelli X *et al.* 2021 The B.1.351 and P.1 variants extend SARS-CoV-2 host range to  
711 mice. *bioRxiv* , 2021.03.18.436013. (doi:10.1101/2021.03.18.436013)
- 712 21. DeLiberto T, Shriner S. 2020 ProMED.
- 713 22. ODA. 2020 Mink at affected Oregon farm negative for SARS-CoV-2, wildlife surveillance  
714 continues. 23 December. See [https://odanews.wpengine.com/mink-at-affected-oregon-](https://odanews.wpengine.com/mink-at-affected-oregon-farm-negative-for-sars-cov-2-wildlife-surveillance-continues/)  
715 [farm-negative-for-sars-cov-2-wildlife-surveillance-continues/](https://odanews.wpengine.com/mink-at-affected-oregon-farm-negative-for-sars-cov-2-wildlife-surveillance-continues/).
- 716 23. Shriner S *et al.* 2021 SARS-CoV-2 Exposure in Escaped Mink, Utah, USA. *Emerging*  
717 *Infectious Disease journal* **27**. (doi:10.3201/eid2703.204444)
- 718 24. Lam SD *et al.* 2020 SARS-CoV-2 spike protein predicted to form complexes with host  
719 receptor protein orthologues from a broad range of mammals. *Sci. Rep.* **10**, 16471.  
720 (doi:10.1038/s41598-020-71936-5)
- 721 25. Liu Z *et al.* 2020 Composition and divergence of coronavirus spike proteins and host ACE2  
722 receptors predict potential intermediate hosts of SARS-CoV-2. *J. Med. Virol.* **92**, 595–601.  
723 (doi:10.1002/jmv.25726)
- 724 26. Luan J, Jin X, Lu Y, Zhang L. 2020 SARS-CoV-2 spike protein favors ACE2 from Bovidae  
725 and Cricetidae. *J. Med. Virol.*
- 726 27. Mathavarajah S, Stoddart AK, Gagnon GA, Dellaire G. 2020 Pandemic danger to the deep:  
727 the risk of marine mammals contracting SARS-CoV-2 from wastewater. ,  
728 2020.08.13.249904. (doi:10.1101/2020.08.13.249904)
- 729 28. Melin AD, Janiak MC, Marrone F 3rd, Arora PS, Higham JP. 2020 Comparative ACE2  
730 variation and primate COVID-19 risk. *Commun Biol* **3**, 641. (doi:10.1038/s42003-020-  
731 01370-w)

- 732 29. Kumar A, Pandey SN, Pareek V, Narayan RK, Faiq MA, Kumari C. 2020 Predicting  
733 susceptibility for SARS-CoV-2 infection in domestic and wildlife animals using ACE2 protein  
734 sequence homology. *Zoo Biol.* (doi:10.1002/zoo.21576)
- 735 30. Huang X, Zhang C, Pearce R, Omenn GS, Zhang Y. 2020 Identifying the Zoonotic Origin of  
736 SARS-CoV-2 by Modeling the Binding Affinity between the Spike Receptor-Binding Domain  
737 and Host ACE2. *J. Proteome Res.* **19**, 4844–4856. (doi:10.1021/acs.jproteome.0c00717)
- 738 31. Ahmed R, Hasan R, Siddiki AMAMZ, Islam MS. 2021 Host range projection of SARS-CoV-  
739 2: South Asia perspective. *Infect. Genet. Evol.* **87**, 104670.  
740 (doi:10.1016/j.meegid.2020.104670)
- 741 32. Damas J *et al.* 2020 Broad host range of SARS-CoV-2 predicted by comparative and  
742 structural analysis of ACE2 in vertebrates. *Proc. Natl. Acad. Sci. U. S. A.* **117**, 22311–  
743 22322. (doi:10.1073/pnas.2010146117)
- 744 33. Ulrich L, Wernike K, Hoffmann D, Mettenleiter TC, Beer M. 2020 Experimental Infection of  
745 Cattle with SARS-CoV-2. *Emerg. Infect. Dis.* **26**, 2979–2981. (doi:10.3201/eid2612.203799)
- 746 34. Sit THC *et al.* 2020 Infection of dogs with SARS-CoV-2. *Nature* **586**, 776–778.  
747 (doi:10.1038/s41586-020-2334-5)
- 748 35. USDA. 2020 Cases of SARS-CoV-2 in animals in the United States. See  
749 [https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/sa\\_one\\_health/sars-cov-2-](https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/sa_one_health/sars-cov-2-animals-us)  
750 [animals-us](https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/sa_one_health/sars-cov-2-animals-us) (accessed on 12 January 2021).
- 751 36. OIE. 2021 Events in animals: OIE - World Organisation for Animal Health. See  
752 [https://www.oie.int/en/scientific-expertise/specific-information-and-](https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019-novel-coronavirus/events-in-animals/)  
753 [recommendations/questions-and-answers-on-2019-novel-coronavirus/events-in-animals/](https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019-novel-coronavirus/events-in-animals/)  
754 (accessed on 28 January 2021).
- 755 37. Shi J *et al.* 2020 Susceptibility of ferrets, cats, dogs, and other domesticated animals to  
756 SARS-coronavirus 2. *Science* **368**, 1016–1020. (doi:10.1126/science.abb7015)
- 757 38. Hamer SA *et al.* 2021 SARS-CoV-2 Infections and Viral Isolations among Serially Tested  
758 Cats and Dogs in Households with Infected Owners in Texas, USA. *Viruses* **13**.  
759 (doi:10.3390/v13050938)
- 760 39. Woolsey C *et al.* 2020 Establishment of an African green monkey model for COVID-19.  
761 *bioRxiv*, 2020.05.17.100289. (doi:10.1101/2020.05.17.100289)
- 762 40. Hall JS *et al.* 2020 Experimental challenge of a North American bat species, big brown bat  
763 (*Eptesicus fuscus*), with SARS-CoV-2. *Transbound. Emerg. Dis.* (doi:10.1111/tbed.13949)
- 764 41. Zhang Q *et al.* 2020 SARS-CoV-2 neutralizing serum antibodies in cats: a serological  
765 investigation. , 2020.04.01.021196. (doi:10.1101/2020.04.01.021196)
- 766 42. San Diego Zoo. 2021 Gorilla Troop at the San Diego Zoo Safari Park Test Positive for  
767 COVID-19. See [https://zoo.sandiegozoo.org/pressroom/news-releases/gorilla-troop-san-](https://zoo.sandiegozoo.org/pressroom/news-releases/gorilla-troop-san-diego-zoo-safari-park-test-positive-covid-19)  
768 [diego-zoo-safari-park-test-positive-covid-19](https://zoo.sandiegozoo.org/pressroom/news-releases/gorilla-troop-san-diego-zoo-safari-park-test-positive-covid-19) (accessed on 28 January 2021).
- 769 43. Rockx B *et al.* 2020 Comparative pathogenesis of COVID-19, MERS, and SARS in a

- 770 nonhuman primate model. *Science* **368**, 1012–1015. (doi:10.1126/science.abb7314)
- 771 44. Munster VJ *et al.* 2020 Respiratory disease in rhesus macaques inoculated with SARS-  
772 CoV-2. *Nature* **585**, 268–272. (doi:10.1038/s41586-020-2324-7)
- 773 45. Sia SF *et al.* 2020 Pathogenesis and transmission of SARS-CoV-2 in golden hamsters.  
774 *Nature* **583**, 834–838. (doi:10.1038/s41586-020-2342-5)
- 775 46. Oreshkova N *et al.* 2020 SARS-CoV-2 infection in farmed minks, the Netherlands, April and  
776 May 2020. *Euro Surveill.* **25**. (doi:10.2807/1560-7917.ES.2020.25.23.2001005)
- 777 47. Freuling CM *et al.* 2020 Susceptibility of Raccoon Dogs for Experimental SARS-CoV-2  
778 Infection. *Emerg. Infect. Dis.* **26**, 2982–2985. (doi:10.3201/eid2612.203733)
- 779 48. Mykytyn AZ *et al.* 2021 Susceptibility of rabbits to SARS-CoV-2. *Emerg. Microbes Infect.*  
780 **10**, 1–7. (doi:10.1080/22221751.2020.1868951)
- 781 49. Bartlett SL *et al.* 2021 SARS-COV-2 INFECTION AND LONGITUDINAL FECAL  
782 SCREENING IN MALAYAN TIGERS (PANTHERA TIGRIS JACKSONI), AMUR TIGERS  
783 (PANTHERA TIGRIS ALTAICA ), AND AFRICAN LIONS (PANTHERA LEO KRUGERI) AT  
784 THE BRONX ZOO, NEW YORK, USA. *J. Zoo Wildl. Med.* **51**, 733–744. (doi:10.1638/2020-  
785 0171)
- 786 50. Wang L *et al.* 2020 Complete Genome Sequence of SARS-CoV-2 in a Tiger from a U.S.  
787 Zoological Collection. *Microbiol Resour Announc* **9**. (doi:10.1128/MRA.00468-20)
- 788 51. Fagre A *et al.* 2021 SARS-CoV-2 infection, neuropathogenesis and transmission among  
789 deer mice: Implications for spillback to New World rodents. *PLoS Pathog.* **17**, e1009585.  
790 (doi:10.1371/journal.ppat.1009585)
- 791 52. Griffin BD *et al.* 2021 SARS-CoV-2 infection and transmission in the North American deer  
792 mouse. *Nat. Commun.* **12**, 3612. (doi:10.1038/s41467-021-23848-9)
- 793 53. Schlottau K *et al.* 2020 SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an  
794 experimental transmission study. *Lancet Microbe* **1**, e218–e225. (doi:10.1016/S2666-  
795 5247(20)30089-6)
- 796 54. Zhao Y *et al.* 2020 Susceptibility of tree shrew to SARS-CoV-2 infection. *Sci. Rep.* **10**,  
797 16007. (doi:10.1038/s41598-020-72563-w)
- 798 55. Louisville Zoo. 2020 Louisville Zoo Female Snow Leopard Tests Positive for SARS-CoV-2.  
799 See [https://louisvillezoo.org/louisville-zoo-female-snow-leopard-tests-positive-for-sars-cov-  
800 2-media-release/](https://louisvillezoo.org/louisville-zoo-female-snow-leopard-tests-positive-for-sars-cov-2-media-release/) (accessed on 28 January 2021).
- 801 56. Ulrich L, Michelitsch A, Halwe N, Wernike K, Hoffmann D, Beer M. 2021 Experimental  
802 SARS-CoV-2 Infection of Bank Voles. *Emerg. Infect. Dis.* **27**, 1193–1195.  
803 (doi:10.3201/eid2704.204945)
- 804 57. Georgia Aquarium. In press. Asian Small-Clawed Otters at Georgia Aquarium Test Positive  
805 for COVID-19. See <http://news.georgiaaquarium.org/stories/releases-20210418> (accessed  
806 on 13 May 2021).

- 807 58. Palmer MV *et al.* 2021 Susceptibility of white-tailed deer (*Odocoileus virginianus*) to SARS-  
808 CoV-2. *bioRxiv.* , 2021.01.13.426628. (doi:10.1101/2021.01.13.426628)
- 809 59. Gryseels S, De Bruyn L, Gyselings R, Calvignac-Spencer S, Leendertz FH, Leirs H. 2020  
810 Risk of human-to-wildlife transmission of SARS-CoV-2. *Mamm. Rev.* **8**, e00373-17.  
811 (doi:10.1111/mam.12225)
- 812 60. Deng W *et al.* 2020 Rhesus macaques can be effectively infected with SARS-CoV-2 via  
813 ocular conjunctival route. *bioRxiv.* , 2020.03.13.990036. (doi:10.1101/2020.03.13.990036)
- 814 61. Rodrigues JPGLM *et al.* 2013 Defining the limits of homology modeling in information-  
815 driven protein docking. *Proteins* **81**, 2119–2128. (doi:10.1002/prot.24382)
- 816 62. Sander C, Schneider R. 1991 Database of homology-derived protein structures and the  
817 structural meaning of sequence alignment. *Proteins* **9**, 56–68.  
818 (doi:10.1002/prot.340090107)
- 819 63. Li Y *et al.* 2020 SARS-CoV-2 and Three Related Coronaviruses Utilize Multiple ACE2  
820 Orthologs and Are Potently Blocked by an Improved ACE2-Ig. *J. Virol.* **94**.  
821 (doi:10.1128/JVI.01283-20)
- 822 64. Fournier D, Luft FC, Bader M, Ganten D, Andrade-Navarro MA. 2012 Emergence and  
823 evolution of the renin-angiotensin-aldosterone system. *J. Mol. Med.* **90**, 495–508.  
824 (doi:10.1007/s00109-012-0894-z)
- 825 65. Han BA, Schmidt JP, Bowden SE, Drake JM. 2015 Rodent reservoirs of future zoonotic  
826 diseases. *Proc. Natl. Acad. Sci. U. S. A.* **112**, 7039–7044. (doi:10.1073/pnas.1501598112)
- 827 66. Yang LH, Han BA. 2018 Data-driven predictions and novel hypotheses about zoonotic tick  
828 vectors from the genus *Ixodes*. *BMC Ecol.* **18**, 7. (doi:10.1186/s12898-018-0163-2)
- 829 67. Han BA, O'Regan SM, Paul Schmidt J, Drake JM. 2020 Integrating data mining and  
830 transmission theory in the ecology of infectious diseases. *Ecol. Lett.* **23**, 1178–1188.  
831 (doi:10.1111/ele.13520)
- 832 68. Han BA, Schmidt JP, Alexander LW, Bowden SE, Hayman DTS, Drake JM. 2016  
833 Undiscovered Bat Hosts of Filoviruses. *PLoS Negl. Trop. Dis.* **10**, e0004815.  
834 (doi:10.1371/journal.pntd.0004815)
- 835 69. Han BA *et al.* 2019 Confronting data sparsity to identify potential sources of Zika virus  
836 spillover infection among primates. *Epidemics* **27**, 59–65.  
837 (doi:10.1016/j.epidem.2019.01.005)
- 838 70. Yang X-L *et al.* 2017 Genetically Diverse Filoviruses in *Rousettus* and *Eonycteris* spp. Bats,  
839 China, 2009 and 2015. *Emerg. Infect. Dis.* **23**, 482–486. (doi:10.3201/eid2303.161119)
- 840 71. Goldstein T *et al.* 2018 The discovery of Bombali virus adds further support for bats as  
841 hosts of ebolaviruses. *Nat Microbiol* **3**, 1084–1089. (doi:10.1038/s41564-018-0227-2)
- 842 72. Sorokina M, M C Teixeira J, Barrera-Vilarmau S, Paschke R, Papatotiriou I, Rodrigues  
843 JPGLM, Kastritis PL. 2020 Structural models of human ACE2 variants with SARS-CoV-2  
844 Spike protein for structure-based drug design. *Sci Data* **7**, 309. (doi:10.1038/s41597-020-

- 845 00652-6)
- 846 73. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. 1990 Basic local alignment search  
847 tool. *J. Mol. Biol.* **215**, 403–410. (doi:10.1016/S0022-2836(05)80360-2)
- 848 74. Winter D. 2017 rentrez: An R package for the NCBI eUtils API. *R J.* **9**, 520.  
849 (doi:10.32614/rj-2017-058)
- 850 75. Rawlings ND, Barrett AJ, Thomas PD, Huang X, Bateman A, Finn RD. 2018 The MEROPS  
851 database of proteolytic enzymes, their substrates and inhibitors in 2017 and a comparison  
852 with peptidases in the PANTHER database. *Nucleic Acids Res.* **46**, D624–D632.  
853 (doi:10.1093/nar/gkx1134)
- 854 76. Katoh K, Misawa K, Kuma K-I, Miyata T. 2002 MAFFT: a novel method for rapid multiple  
855 sequence alignment based on fast Fourier transform. *Nucleic Acids Res.* **30**, 3059–3066.  
856 (doi:10.1093/nar/gkf436)
- 857 77. Lan J *et al.* 2020 Structure of the SARS-CoV-2 spike receptor-binding domain bound to the  
858 ACE2 receptor. *Nature* **581**, 215–220. (doi:10.1038/s41586-020-2180-5)
- 859 78. Webb B, Sali A. 2016 Comparative Protein Structure Modeling Using MODELLER. *Curr.*  
860 *Protoc. Bioinformatics* **54**, 5.6.1–5.6.37. (doi:10.1002/cpbi.3)
- 861 79. Sali A, Blundell TL. 1993 Comparative protein modelling by satisfaction of spatial restraints.  
862 *J. Mol. Biol.* **234**, 779–815. (doi:10.1006/jmbi.1993.1626)
- 863 80. van Zundert GCP *et al.* 2016 The HADDOCK2.2 Web Server: User-Friendly Integrative  
864 Modeling of Biomolecular Complexes. *J. Mol. Biol.* **428**, 720–725.  
865 (doi:10.1016/j.jmb.2015.09.014)
- 866 81. de Magalhães JP, Costa J. 2009 A database of vertebrate longevity records and their  
867 relation to other life-history traits. *J. Evol. Biol.* **22**, 1770–1774. (doi:10.1111/j.1420-  
868 9101.2009.01783.x)
- 869 82. Myhrvold NP, Baldrige E, Chan B, Sivam D, Freeman DL, Ernest SKM. 2015 An amniote  
870 life-history database to perform comparative analyses with birds, mammals, and reptiles:  
871 Ecological ArchivesE096-269. *Ecology* **96**, 3109–3000. (doi:10.1890/15-0846r.1)
- 872 83. Wilman H, Belmaker J, Simpson J, de la Rosa C, Rivadeneira MM, Jetz W. 2014  
873 EltonTraits 1.0: Species-level foraging attributes of the world's birds and mammals. *Ecology*  
874 **95**, 2027–2027. (doi:10.1890/13-1917.1)
- 875 84. Dallas T, Park AW, Drake JM. 2017 Predicting cryptic links in host-parasite networks. *PLoS*  
876 *Comput. Biol.* **13**, e1005557. (doi:10.1371/journal.pcbi.1005557)
- 877 85. Baker C. 2018 *wosr: Clients to the 'Web of Science' and 'InCites' APIs*. See  
878 <https://CRAN.R-project.org/package=wosr>.
- 879 86. Bosco-Lauth AM *et al.* 2020 Experimental infection of domestic dogs and cats with SARS-  
880 CoV-2: Pathogenesis, transmission, and response to reexposure in cats. *Proc. Natl. Acad.*  
881 *Sci. U. S. A.* **117**, 26382–26388. (doi:10.1073/pnas.2013102117)

- 882 87. Elith J, Leathwick JR, Hastie T. 2008 A working guide to boosted regression trees. *J. Anim.*  
883 *Ecol.* **77**, 802–813.
- 884 88. Jones KE *et al.* 2009 PanTHERIA: a species-level database of life history, ecology, and  
885 geography of extant and recently extinct mammals: Ecological Archives E090-184. *Ecology*  
886 **90**, 2648–2648. (doi:10.1890/08-1494.1)
- 887 89. Wilson DE, Reeder DM. 2005 *Mammal Species of the World: A Taxonomic and Geographic*  
888 *Reference*. Baltimore, MD: JHU Press. See  
889 <http://books.google.com/books?id=JgAMbNSt8ikC>.
- 890 90. Greenwell B, Boehmke B, Cunningham J, Developers GBM. 2020 *Generalized Boosted*  
891 *Regression Models*. Comprehensive R Archive Network (CRAN). See [https://cran.r-](https://cran.r-project.org/web/packages/gbm/index.html)  
892 [project.org/web/packages/gbm/index.html](https://cran.r-project.org/web/packages/gbm/index.html).
- 893 91. R Core Team. 2020 *R: A language and environment for statistical computing*. Vienna,  
894 Austria. See <http://www.R-project.org/>.
- 895 92. Wilkins AS, Wrangham RW, Fitch WT. 2014 The ‘domestication syndrome’ in mammals: a  
896 unified explanation based on neural crest cell behavior and genetics. *Genetics* **197**, 795–  
897 808. (doi:10.1534/genetics.114.165423)
- 898 93. Cleaveland S, Laurenson MK, Taylor LH. 2001 Diseases of humans and their domestic  
899 mammals: pathogen characteristics, host range and the risk of emergence. *Philos. Trans.*  
900 *R. Soc. Lond. B Biol. Sci.* **356**, 991–999. (doi:10.1098/rstb.2001.0889)
- 901 94. Database MD. 2020 *Mammal Diversity Database*. (doi:10.5281/zenodo.4139818)
- 902 95. IUCN. 2020 The IUCN Red List of Threatened Species.
- 903 96. Liu Y *et al.* 2021 Functional and genetic analysis of viral receptor ACE2 orthologs reveals a  
904 broad potential host range of SARS-CoV-2. *Proc. Natl. Acad. Sci. U. S. A.* **118**.  
905 (doi:10.1073/pnas.2025373118)
- 906 97. Pitra C, Schwarz S, Fickel J. 2010 Going west—invasion genetics of the alien raccoon dog  
907 *Nyctereutes procynoides* in Europe. *Eur. J. Wildl. Res.* **56**, 117–129. (doi:10.1007/s10344-  
908 009-0283-2)
- 909 98. Milla R *et al.* 2018 Phylogenetic patterns and phenotypic profiles of the species of plants  
910 and mammals farmed for food. *Nat Ecol Evol* **2**, 1808–1817. (doi:10.1038/s41559-018-  
911 0690-4)
- 912 99. Kevany S. 2020 Danish Covid mink cull and future disease fears will kill fur trade, say  
913 farmers. *The Guardian*, 6 November. See  
914 [http://www.theguardian.com/environment/2020/nov/06/danish-covid-mink-cull-and-future-](http://www.theguardian.com/environment/2020/nov/06/danish-covid-mink-cull-and-future-disease-fears-will-kill-fur-trade-say-farmers)  
915 [disease-fears-will-kill-fur-trade-say-farmers](http://www.theguardian.com/environment/2020/nov/06/danish-covid-mink-cull-and-future-disease-fears-will-kill-fur-trade-say-farmers).
- 916 100. Can ÖE, D’Cruze N, Macdonald DW. 2019 Dealing in deadly pathogens: Taking stock of  
917 the legal trade in live wildlife and potential risks to human health. *Glob Ecol Conserv* **17**,  
918 e00515. (doi:10.1016/j.gecco.2018.e00515)
- 919 101. Lam TT-Y *et al.* 2020 Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins.



- 920 *Nature* **583**, 282–285. (doi:10.1038/s41586-020-2169-0)
- 921 102. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. 2020 The proximal origin of  
922 SARS-CoV-2. *Nat. Med.* **26**, 450–452. (doi:10.1038/s41591-020-0820-9)
- 923 103. Lehmann D, Halbwax ML, Makaga L, Whytock R, Ndindiwe Malata L, Bombenda Mouele  
924 W, Momboua BR, Koumba Pambo AF, White LJT. 2020 Pangolins and bats living together  
925 in underground burrows in Lopé National Park, Gabon. *Afr. J. Ecol.* (doi:10.1111/aje.12759)
- 926 104. Tsuda S *et al.* 2012 Genomic and serological detection of bat coronavirus from bats in the  
927 Philippines. *Arch. Virol.* **157**, 2349–2355. (doi:10.1007/s00705-012-1410-z)
- 928 105. Olival KJ *et al.* 2020 Possibility for reverse zoonotic transmission of SARS-CoV-2 to free-  
929 ranging wildlife: A case study of bats. *PLoS Pathog.* **16**, e1008758.  
930 (doi:10.1371/journal.ppat.1008758)
- 931 106. Anthony SJ *et al.* 2013 Coronaviruses in bats from Mexico. *J. Gen. Virol.* **94**, 1028–1038.  
932 (doi:10.1099/vir.0.049759-0)
- 933 107. Anthony SJ *et al.* 2017 Global patterns in coronavirus diversity. *Virus Evol* **3**, vex012.  
934 (doi:10.1093/ve/vex012)
- 935 108. Zhou H *et al.* 2020 A Novel Bat Coronavirus Closely Related to SARS-CoV-2 Contains  
936 Natural Insertions at the S1/S2 Cleavage Site of the Spike Protein. *Curr. Biol.* **30**, 2196–  
937 2203.e3. (doi:10.1016/j.cub.2020.05.023)
- 938 109. Hul V *et al.* 2021 A novel SARS-CoV-2 related coronavirus in bats from Cambodia. *bioRxiv.*  
939 , 2021.01.26.428212. (doi:10.1101/2021.01.26.428212)
- 940 110. Mou H *et al.* 2020 Mutations from bat ACE2 orthologs markedly enhance ACE2-Fc  
941 neutralization of SARS-CoV-2. *bioRxiv.* , 2020.06.29.178459.  
942 (doi:10.1101/2020.06.29.178459)
- 943 111. Wacharapluesadee S *et al.* 2021 Evidence for SARS-CoV-2 related coronaviruses  
944 circulating in bats and pangolins in Southeast Asia. *Nat. Commun.* **12**, 972.  
945 (doi:10.1038/s41467-021-21240-1)
- 946 112. Pulliam JRC *et al.* 2012 Agricultural intensification, priming for persistence and the  
947 emergence of Nipah virus: a lethal bat-borne zoonosis. *J. R. Soc. Interface* **9**, 89–101.  
948 (doi:10.1098/rsif.2011.0223)
- 949 113. Plowright RK *et al.* 2015 Ecological dynamics of emerging bat virus spillover. *Proceedings*  
950 *of the Royal Society B.* **282**, 20142124. (doi:10.1098/rspb.2014.2124)
- 951 114. Kessler MK *et al.* 2018 Changing resource landscapes and spillover of henipaviruses. *Ann.*  
952 *N. Y. Acad. Sci.* **1429**, 78–99. (doi:10.1111/nyas.13910)
- 953 115. Peel AJ, Field HE, Aravena MR, Edson D, McCallum H, Plowright RK, Prada D. 2020  
954 Coronaviruses and Australian bats: a review in the midst of a pandemic. *Aust. J. Zool.*  
955 (doi:10.1071/ZO20046)
- 956 116. Bordes F, Blasdel K, Morand S. 2015 Transmission ecology of rodent-borne diseases:

- 957 New frontiers. *Integr. Zool.* **10**, 424–435. (doi:10.1111/1749-4877.12149)
- 958 117. Ostfeld RS, Canham CD, Oggenfuss K, Winchcombe RJ, Keesing F. 2006 Climate, deer,  
959 rodents, and acorns as determinants of variation in lyme-disease risk. *PLoS Biol.* **4**, e145.  
960 (doi:10.1371/journal.pbio.0040145)
- 961 118. Machtinger ET, Williams SC. 2020 Practical Guide to Trapping *Peromyscus leucopus*  
962 (Rodentia: Cricetidae) and *Peromyscus maniculatus* for Vector and Vector-Borne Pathogen  
963 Surveillance and Ecology. *J. Insect Sci.* **20**. (doi:10.1093/jisesa/ieaa028)
- 964 119. Morand S *et al.* 2015 Global parasite and *Rattus* rodent invasions: The consequences for  
965 rodent-borne diseases. *Integr. Zool.* **10**, 409–423. (doi:10.1111/1749-4877.12143)
- 966 120. Hamdan NES, Ng YL, Lee WB, Tan CS, Khan FAA, Chong YL. 2017 Rodent Species  
967 Distribution and Hantavirus Seroprevalence in Residential and Forested areas of Sarawak,  
968 Malaysia. *Trop Life Sci Res* **28**, 151–159. (doi:10.21315/tlsr2017.28.1.11)
- 969 121. Louys J, Herrera MB, Thomson VA, Wiewel AS, Donnellan SC, O'Connor S, Aplin K. 2020  
970 Expanding population edge craniometrics and genetics provide insights into dispersal of  
971 commensal rats through Nusa Tenggara, Indonesia. *Rec. Aust. Mus.* **72**, 287–302.  
972 (doi:10.3853/j.2201-4349.72.2020.1730)
- 973 122. Tadin A *et al.* 2016 Molecular Survey of Zoonotic Agents in Rodents and Other Small  
974 Mammals in Croatia. *Am. J. Trop. Med. Hyg.* **94**, 466–473. (doi:10.4269/ajtmh.15-0517)
- 975 123. Yousefi A, Eslami A, Mobedi I, Rahbari S, Ronaghi H. 2014 Helminth Infections of House  
976 Mouse (*Mus musculus*) and Wood Mouse (*Apodemus sylvaticus*) from the Suburban Areas  
977 of Hamadan City, Western Iran. *Iran. J. Parasitol.* **9**, 511–518.
- 978 124. Rahman MM, Yoon KB, Lim SJ, Jeon MG, Kim HJ, Kim HY, Cho JY, Chae HM, Park YC.  
979 2017 Molecular detection by analysis of the 16S rRNA gene of fecal coliform bacteria from  
980 the two Korean *Apodemus* species (*Apodemus agrarius* and *A. peninsulae*). *Genet. Mol.*  
981 *Res.* **16**. (doi:10.4238/gmr16029510)
- 982 125. Bertolino S, Lurz PWW. 2013 *Callosciurus* squirrels: worldwide introductions, ecological  
983 impacts and recommendations to prevent the establishment of new invasive populations:  
984 Worldwide introductions of *Callosciurus* squirrels. *Mamm. Rev.* **43**, 22–33.  
985 (doi:10.1111/j.1365-2907.2011.00204.x)
- 986 126. Mildenstein T, Tanshi I, Racey PA. 2016 Exploitation of Bats for Bushmeat and Medicine. In  
987 *Bats in the Anthropocene: Conservation of Bats in a Changing World* (eds CC Voigt, T  
988 Kingston), pp. 325–375. Cham: Springer International Publishing. (doi:10.1007/978-3-319-  
989 25220-9\_12)
- 990 127. Ransaleleh TA, Nangoy MJ, Wahyuni I, Lomboan A, Koneri R, Saputro S, Pamungkas J,  
991 Latinne A. 2020 Identification of bats on traditional market in dumoga district, North  
992 Sulawesi. *IOP Conf. Ser.: Earth Environ. Sci.* **473**, 012067. (doi:10.1088/1755-  
993 1315/473/1/012067)
- 994 128. Tampon NVT, Rabaya YMC, Malbog KMA, Burgos SC, Libre K Jr, Valila ASD, Achondo  
995 MJMM, Onggo LS, Murao LAE. 2020 First molecular evidence for bat betacoronaviruses in

- 996 Mindanao. *Philipp J. Sci.* **149**, 91–94.
- 997 129. Logeot M, Mauroy A, Thiry E, De Regge N, Vervaeke M, Beck O, De Waele V, Van den  
998 Berg T. 2021 Risk assessment of SARS-CoV-2 infection in free-ranging wild animals in  
999 Belgium. *Transbound. Emerg. Dis.* (doi:10.1111/tbed.14131)
- 1000 130. Weber A, Kalema-Zikusoka G, Stevens NJ. 2020 Lack of Rule-Adherence During Mountain  
1001 Gorilla Tourism Encounters in Bwindi Impenetrable National Park, Uganda, Places Gorillas  
1002 at Risk From Human Disease. *Front Public Health* **8**, 1. (doi:10.3389/fpubh.2020.00001)
- 1003 131. Barbosa A *et al.* 2021 Risk assessment of SARS-CoV-2 in Antarctic wildlife. *Sci. Total*  
1004 *Environ.* **755**, 143352. (doi:10.1016/j.scitotenv.2020.143352)
- 1005 132. Gibbons A. 2021 Captive gorillas test positive for coronavirus. *Science*  
1006 (doi:10.1126/science.abg5458)
- 1007 133. Daly N. 2021 First great apes at U.S. zoo receive COVID-19 vaccine made for animals.  
1008 *National Geographic* See [https://www.nationalgeographic.com/animals/article/first-great-](https://www.nationalgeographic.com/animals/article/first-great-apes-at-us-zoo-receive-coronavirus-vaccine-made-for-animals)  
1009 [apes-at-us-zoo-receive-coronavirus-vaccine-made-for-animals](https://www.nationalgeographic.com/animals/article/first-great-apes-at-us-zoo-receive-coronavirus-vaccine-made-for-animals).
- 1010 134. Aleccia J. 2020 'The Biggest Nemesis': Black-Footed Ferrets Get Experimental  
1011 Coronavirus Vaccine. *Kaiser Health News*, 27 December. See  
1012 [https://www.cpr.org/2020/12/27/the-biggest-nemesis-black-footed-ferrets-get-experimental-](https://www.cpr.org/2020/12/27/the-biggest-nemesis-black-footed-ferrets-get-experimental-coronavirus-vaccine/)  
1013 [coronavirus-vaccine/](https://www.cpr.org/2020/12/27/the-biggest-nemesis-black-footed-ferrets-get-experimental-coronavirus-vaccine/).
- 1014 135. Xu L *et al.* 2020 COVID-19-like symptoms observed in Chinese tree shrews infected with  
1015 SARS-CoV-2. *Zool Res* **41**, 517–526. (doi:10.24272/j.issn.2095-8137.2020.053)
- 1016 136. Becker DJ, Washburne AD, Faust CL, Pulliam JRC, Mordecai EA, Lloyd-Smith JO,  
1017 Plowright RK. 2019 Dynamic and integrative approaches to understanding pathogen  
1018 spillover. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **374**, 20190014.  
1019 (doi:10.1098/rstb.2019.0014)
- 1020 137. Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, Lloyd-Smith JO.  
1021 2017 Pathways to zoonotic spillover. *Nat. Rev. Microbiol.* (doi:10.1038/nrmicro.2017.45)
- 1022 138. Morris DH *et al.* 2020 The effect of temperature and humidity on the stability of SARS-CoV-  
1023 2 and other enveloped viruses. *bioRxiv* (doi:10.1101/2020.10.16.341883)
- 1024 139. Bean AGD, Baker ML, Stewart CR, Cowled C, Deffrasnes C, Wang L-F, Lowenthal JW.  
1025 2013 Studying immunity to zoonotic diseases in the natural host - keeping it real. *Nat. Rev.*  
1026 *Immunol.* **13**, 851–861. (doi:10.1038/nri3551)
- 1027 140. Letko M, Seifert SN, Olival KJ, Plowright RK, Munster VJ. 2020 Bat-borne virus diversity,  
1028 spillover and emergence. *Nat. Rev. Microbiol.* **18**, 461–471. (doi:10.1038/s41579-020-  
1029 0394-z)
- 1030 141. Sawatzki K, Hill NJ, Puryear WB, Foss AD, Stone JJ, Runstadler JA. 2021 Host barriers to  
1031 SARS-CoV-2 demonstrated by ferrets in a high-exposure domestic setting. *Proc. Natl.*  
1032 *Acad. Sci. U. S. A.* **118**. (doi:10.1073/pnas.2025601118)
- 1033 142. Ruiz-Arrondo I, Portillo A, Palomar AM, Santibanez S, Santibanez P, Cervera C, Oteo JA.

- 1034 2020 Detection of SARS-CoV-2 in pets living with COVID-19 owners diagnosed during the  
1035 COVID-19 lockdown in Spain: A case of an asymptomatic cat with SARS-CoV-2 in Europe.  
1036 *bioRxiv*. (doi:10.1101/2020.05.14.20101444)
- 1037 143. Peel AJ *et al.* 2019 Synchronous shedding of multiple bat paramyxoviruses coincides with  
1038 peak periods of Hendra virus spillover. *Emerg. Microbes Infect.* **8**, 1314–1323.  
1039 (doi:10.1080/22221751.2019.1661217)
- 1040 144. Restif O *et al.* 2012 Model-guided fieldwork: practical guidelines for multidisciplinary  
1041 research on wildlife ecological and epidemiological dynamics. *Ecol. Lett.*  
1042 (doi:10.1111/j.1461-0248.2012.01836.x)
- 1043 145. Cook JA *et al.* 2020 Integrating Biodiversity Infrastructure into Pathogen Discovery and  
1044 Mitigation of Emerging Infectious Diseases. *Bioscience* **70**, 531–534.  
1045 (doi:10.1093/biosci/biaa064)
- 1046 146. Thompson CW *et al.* 2021 Preserve a Voucher Specimen! The Critical Need for Integrating  
1047 Natural History Collections in Infectious Disease Studies. *MBio* **12**.  
1048 (doi:10.1128/mBio.02698-20)
- 1049
- 1050
- 1051
- 1052
- 1053