Targeting surveillance in apparently healthy versus diseased wild mammals for zoonotic virus discovery

How to find the next zoonotic virus

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Keywords

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- surveillance
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Abbreviations
- EID: Emerging Infectious Diseases
- ICTV: International Committee on the Taxonomy of Viruses
- PCR: Polymerase Chain Reaction

Abstract
We analyzed a database of mammal-virus associations to ask whether zoonotic disease surveillance targeting diseased animals is the best strategy to identify potentially zoonotic pathogens. Though a mixed healthy and diseased surveillance strategy is generally best, surveillance of apparently healthy bats and rodents would likely maximize discovery potential for most zoonotic viruses.

Impact statement
Bats and rodents can harbor viruses that are potentially harmful to humans. In order to find new viruses that may pose a threat to humans, it is better to survey healthy bats and rodents for viruses than apparently diseased bats and rodents.

Introduction
Nearly two-thirds of emerging infectious diseases (EIDs) (Eidson, et al. 2001) that affect humans are zoonotic, and three-quarters of these originate in wildlife, making surveillance of wildlife for novel pathogens part of a logical strategy to prevent future zoonotic EIDs (Taylor, Latham and Woolhouse 2001, Jones, et al. 2008, Woolhouse and Gowtage-Sequeria 2005, USAID 2009). In this study, we adhere to the following definition of an Emerging Infectious Disease:

> *Infectious diseases whose incidence in humans has increased in the past 2 decades or threatens to increase in the near future have been defined as 'emerging.' These diseases, which respect no national boundaries, include: new infections resulting from changes or evolution of existing organisms, known infections spreading to new geographic areas or populations, previously unrecognized infections appearing in areas undergoing ecologic transformation, and old infections reemerging as a result of antimicrobial resistance in known agents or breakdowns in public health measures.*
>
> *—The Centers for Disease Control and Prevention*

With respect to zoonotic virus discovery, Simon Anthony said, "we could feasibly find most of the viruses that exist in mammals in the next 20 years". Wildlife are thought to harbor a high diversity of unknown pathogens, but global characterization of this diversity would be costly

and logistically challenging (Morse 1993, 25-50). Given limited resources for pandemic prevention, there is public health benefit in focusing pathogen discovery on those species most likely to harbor novel zoonoses (Woolhouse and Gowtage-Sequeria 2005, USAID 2009). One strategy to maximize the likelihood of discovering novel pathogens is surveillance of animal die-offs, outbreaks in wildlife, or diseased wildlife. Here, we analyze a database of known zoonotic viruses in mammal hosts to answer the driving question of whether we should stratify surveillance strategies (i.e. visibly diseased versus apparently healthy animals) by wildlife host groups to best detect novel pathogens with zoonotic potential. In answering this question, we can better determine how host and virus taxonomy might influence our decisions about applying limited surveillance resources to a growing global health problem (Morse 1993, chap. 2).

Methods

We focused our analysis on mammalian hosts and viruses as they are more likely to be associated with human EIDs than any other host-pathogen type (Cleaveland, Laurenson and Taylor 2001, Woolhouse and Gowtage-Sequeria 2005). We constructed a database of all human emerging viruses previously identified as originating in wildlife (Jones, et al. 2008), supplemented with all zoonotic viruses from the International Committee on the Taxonomy of Viruses (ICTV) database (www.ictvdb.org) with non-human, mammalian hosts (Supporting Dataset 1). For each zoonotic virus, we conducted a literature search for reports of infection in any mammalian host, using virus name and relevant synonyms (www.ictvdb.org) as keywords in ISI Web of Knowledge, Wildlife Disease Association Meeting Abstracts, Google Scholar, and the Global Mammal Parasites Database (www.mammalparasites.org). The resulting 605 host-pathogen relationships included 56 unique viruses from 17 viral families and 325 unique mammals from 15 orders[4].

Literature search

We then conducted a secondary literature search to determine whether viruses in our database cause signs of disease in their wildlife hosts, using an aggregate of all publications available on PubMed, ISI Web of Science, BIOSIS Previews, and Biological and Agricultural Index Plus, with search terms consisting of virus names and ICTV synonyms, host genus and species names and common names (reconciled to the 2005 version of Mammal Species of the World (Wilson and Reeder 2005)). All resulting abstracts and available full text reports were examined until the first 'robust' report of visible disease was encountered. A report was considered 'robust' only if infections were confirmed by PCR analysis or virus isolation and clinical signs were explicitly recorded to have occurred during active infection. We excluded studies only reporting serology because of potential cross-reactivity among related viruses and poor correlation between serologic status and concurrent infection. For mammal-virus pairs without visible disease the search was exhaustive. See Methods for more.

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[4]We excluded rabies from our analysis because the intense research effort on this virus and its high pathogenicity in almost all of its wide range of hosts (The Center for Food Security & Public Health; Institute for International Cooperation in Animal Biologics; World Organisation for Animal Health 2009) would skew the data disproportionately.

Virus ID

Viruses were identified as causing visible disease in a host if individual or epizootic mortality, or grossly visible or otherwise observable signs of morbidity such as high fever, loss of mobility, or severe reduction in body condition were reported. We considered diseases to be nonpathogenic in their hosts only if actively infected animals were explicitly reported to be free of visible disease. Animals with less clear signs such as nasal discharge or neonatal mortality were not considered 'asymptomatic' because of the low detection probability associated with these traits in wild mammal surveillance. We rejected reports of experimentally induced disease because of the risk that dosage and inoculation technique would not be consistent with naturally occurring infections. However, we included experimental studies if actively infected animals remained asymptomatic, with the assumption that clinical signs of infection were most likely to be seen in animals monitored in laboratory settings than in the wild, and that stressful conditions in captivity would heighten the likelihood of a normally benign pathogen leading to clinical signs (Williams and Barker 2008). Furthermore, experimental infections often involve more direct routes of inoculation than naturally occurring infections, and are therefore more likely to induce disease.

We first determined the percentage of reports of host-virus pairs in which observable disease was described, 'Symptomatic', no observable disease was described, 'Asymptomatic', or no description of disease was included, 'No data'. We plotted the results in a pie chart using the default `pie` function and the `RColorBrewer` library (Code 1).

Code 1. R code. Authors: Dr. Tiffany L Bogich, PhD (EEB)[5,6]. License: CC0-1.0.

```
rm(list=ls())
library(RColorBrewer)

counts<-c(293,88,224)
pc<-c("48%","15%","37%")
labs<-c("No Data","Symptomatic","Asymptomatic")

#piechart of all drivers
postscript("~/12-1042-F1A.eps", width=5, height=4,pointsize=10, onefile=FALSE, horizontal=FALSE,
paper="special")
par(mar=c(2,0,1.5,0))
pie(counts, labels=pc, ps=14,edges=400,radius=0.5, col=brewer.pal(9,"Greys")[c(1,3,6)],lty=1,lwd=1, init.angle=-90)
legend(0.6,-0.1, labs,col=brewer.pal(9,"Greys")[c(1,3,6)],fill=brewer.pal(9,"Greys")[c(1,3,6)],bty="n",cex=0.9)
dev.off()
```

We then conducted a logistic regression analysis of host apparent disease as a function of host taxonomic group and virus taxonomy for the subset of mammal-virus pairs for which the host order or virus family had at least 3 records in the database using Firth's bias reduction

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[6]Wrote the code.

procedure (Firth 1993) in R statistical software package 'brglm' (R v2.15-2) and the I function for the removal of the leading $O(n^{-1})$ term from the asymptotic expansion of the bias of the maximum likelihood estimator (Equation 1).

Equation 1. Authors: Dr. Tiffany L Bogich, PhD(EEB)[7].

$$y_{diseaseStatus} \sim x_{virusFamily} + x_{hostOrder} + e$$

We then calculated odds ratios for each host order and virus family relative to the reference categories (Flaviviridae and Artiodactyla) and the predicted probability of being symptomatic for all species order-virus family combinations.

[7]Wrote the equation.

Results

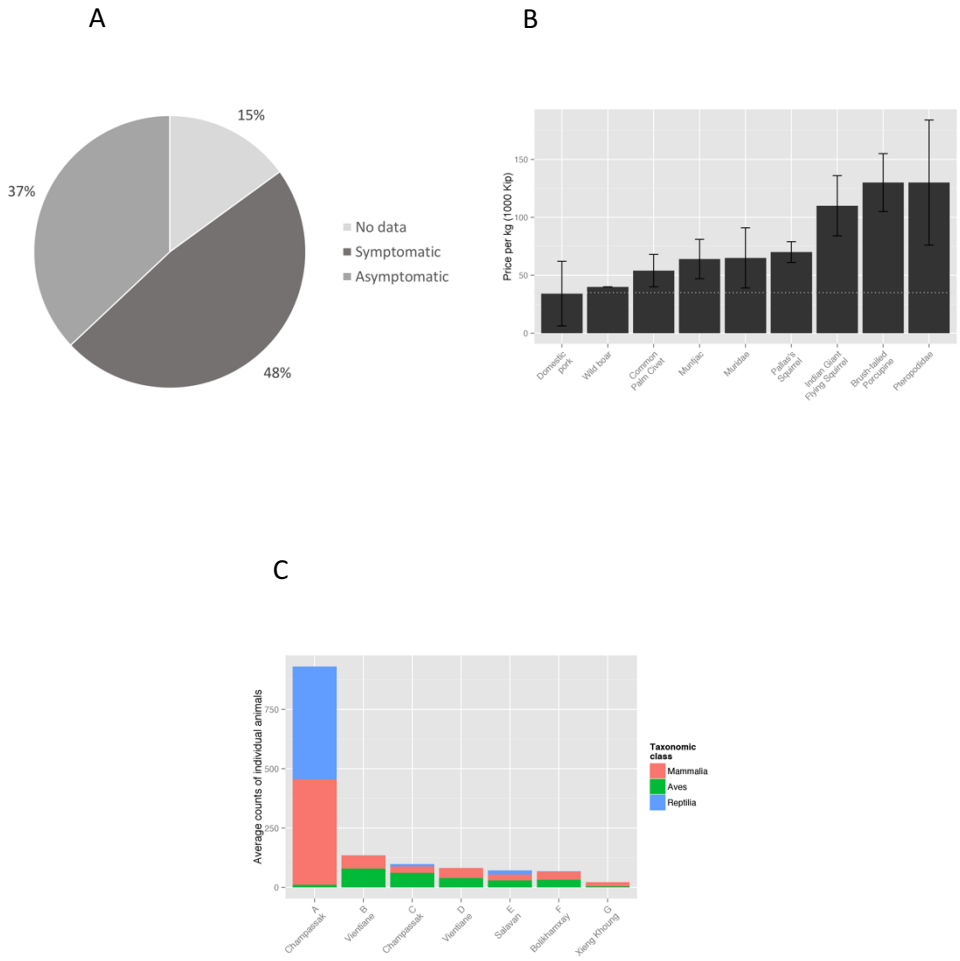

Figure 1. Authors: Ms. Jordan Levinson, MSc[8];Dr. Tiffany L Bogich, PhD[9]. License: CC0-1.0. Code from: Code 1. Data from: Supporting Figure 1. (A) Percentage of reports of host-virus pairs in which observable disease was described. (B) The total number of each host order or virus family included in the database is given above each bar. (C) The proportion of virus families for which hosts are reported symptomatic are given with standard error bars, calculated assuming binomial error structure.

Our search of 605 mammal-virus associations investigated yielded explicit information on host health in 52% of the 312 mammal-virus pairs. Of these, approximately 28% of infected wildlife hosts were reported to present with visible disease (n = 88) and 72% (n = 224) were reported without evidence of visible disease (Figure 1A). The proportion of hosts that were symptomatic differed across host order (Figure 1B), virus family (Figure 1C), and geographic location (Supporting Figure 2).

[8]Prepared the figure.
[9]Created the study.

We found that virus family and host order were significant predictors of disease status (χ^2=88.70, p<0.001 and χ^2=59.45, p<0.001, respectively). A preview is provided in Video 1. Species infected with paramyxoviruses, poxviruses, and reoviruses were more likely to be visibly diseased whereas species infected with bunyaviruses were less likely to be visibly diseased relative to the reference category. Hosts infected with filoviruses were marginally more likely to be visibly diseased (Table 1).

video.mp4

Video 1. Cross-sectional view of a virus. Author: Kevin J Olival, PhD. Reproduced from: (McQuarrie 1995). License: CC0-1.0.

Table 1. Logistic regression analysis with bias reduction of whether a host presents with disease for 234 mammal–virus pairs from 5 taxonomic orders of mammals and 10 taxonomic families of viruses. The subset of data used was selected by using a cutoff of at least 3 records in the database to avoid making inference about host orders or virus families, for which we had very little information. Authors: Kevin J Olival, PhD[10]; Prof. Christine Kreuder Johnson, DVM, MPVM, PhD[11]. Code from: Supporting Code 1. License: CC0-1.0.

Predictor[12]	Coefficient	SE	Test statistic (Z)	p-value	OR	95% CI
Constant	-0.33	0.58	-0.56	0.58	0.72	(0.23, 2.26)
Virus Family (Reference category: Flaviviridae)						
Bunyaviridae	-1.74	0.64	-2.71	0.01	0.18	(0.05, 0.62)
Filoviridae	3.26	1.83	1.78	0.08	26.07	(0.72, 944.49)
Herpesviridae	0.10	0.65	0.16	0.87	1.11	(0.31, 3.94)
Paramyxoviridae	3.43	1.42	2.41	0.02	30.95	(1.90, 503.52)
Picornaviridae	1.12	0.76	1.48	0.14	3.08	(0.69, 13.68)
Poxviridae	2.29	0.81	2.82	<0.001	9.90	(2.01, 48.72)
Reoviridae	2.13	1.05	2.02	0.04	8.39	(1.07, 66.12)
Rhabdoviridae	9.20	2.39	3.85	<0.001	NA[13]	NA[13]
Togaviridae	-0.36	0.63	-0.58[13]	0.56	0.70	(0.20, 2.38)
Species Order (Reference category: Artiodactyla)						
Chiroptera	-6.47	1.81	-3.57[13]	<0.001	0.00	(0.00, 0.05)
Perissodactyla	0.58	0.76	0.77	0.44	1.79	(0.40, 8.03)
Primates	-0.16	0.68	-0.24	0.81	0.85	(0.22, 3.24)
Rodentia	-1.12	0.67	-1.66	0.10	0.33	(0.09, 1.22)

Species in the order Chiroptera (e.g. *Pipistrellus pipistrellus*) were less likely to be visibly diseased and species in the order Rodentia were marginally less likely to be visibly diseased, relative to the reference category (Table 1). Species in the order Chiroptera have a lower probability of visible disease than in other orders (Figure 2), though **all Chiroptera infected with**

[10]Conducted the analysis.
[11] Senior author.
[12]Virus and host reference groups were selected as those for which sample size was sufficiently large and symptomatic infection was moderate (see Figure 1).
[13]All host–virus pairs were symptomatic.

non-rabies rhabdoviruses have a high probability of visible disease. In the dataset, all host-pairs with rhabdoviruses were found in Chiroptera and were reported with visible disease in that host (Figure 1).

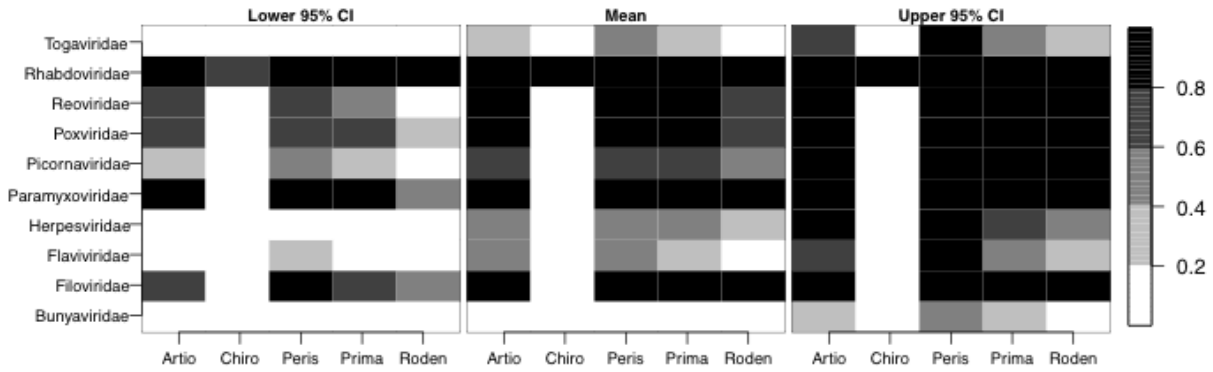

Figure 2. The probability of being symptomatic based on a logistic regression analysis with bias reduction of whether or not a host presents with disease for 234 mammal-virus pairs from 5 orders of mammals and 10 families of viruses, including the lower 95% confidence interval (left), mean (center), and upper 95% confidence interval (right). Probabilities are based on the predicted values of the logistic regression and are given on a five-point gray scale from white (0.0 – 0.2) to black (0.8 - 1.0). Confidence values were calculated as the coefficient plus 1.96 times the standard error. Authors: Dr. Tiffany L Bogich, PhD (NIH)[14]; Ms. Jordan Levinson, MSc[15]; Prof. Christine Kreuder Johnson, DVM, MPVM, PhD[16]. Contributors: Kevin J Olival, PhD[8]. License: CC0-1.0. Data from: Table 1; Supporting Table 1.

Conclusions

Our data suggest that Chiroptera and Rodentia, two of the three main mammalian orders often targeted for zoonotic disease surveillance (the third being non-human primates (Leendertz, et al. 2006, Wolfe, Daszak, et al. 2005, Wolfe, Escalante, et al. 1998) are less likely to present with visible disease than other orders (Figure 1). The mechanism behind this relationship is an important area for additional research. Generally, we found that the probability of presenting with visible disease depends on the host and virus taxonomy, and the only host order for which

Text Box 1. Surveillance for West Nile virus with crow deaths. Author: Dr. Tiffany L Bogich, PhD. License: CC0-1.0.

Crow deaths were used as a sentinel surveillance system for West Nile virus detection in the northeastern part of the United States during the outbreak in the summer and fall of 1999 (Eidson, et al. 2001). From August to December 1999, 295 dead birds weere laboratory-confirmed with West Nile virus infection 89% of which were American Crows (*Corvus brachyrhynochos*). The complete genome of the West Nile virus isolated from crows is available on GenBank (The Broad Institute Genomics Platform; The Broad Institute Genome Sequencing Center for Infectious Disease 2014)(accession number KJ501319.1) . Bird deaths were critical in identifying West Nile virus (Supporting Dataset 2) outbreak and provided a sensitive method of detecting West Nile virus ahead of

[14]Conducted the analysis.
[15]Collected the data.
[16] Prepared the figures.

a single strategy (in this case healthy animal surveillance) can be applied across nearly all virus families (excluding Rhabdoviridae) is for Chiroptera. Therefore, particularly for the case of novel virus detection, our results point to a mixed strategy of targeted syndromic and healthy animal surveillance across host and virus taxonomies. A mixed strategy could combine apparently healthy animal surveillance (particularly in Chiroptera) with syndromic surveillance in other wildlife and domestic animal hosts, as syndromic surveillance has previously proven useful where secondary animal hosts are involved (e.g. surveillance for West Nile virus (Eidson, et al. 2001), henipaviruses (Mohd, Gan and Ong 2000, Selvey, et al. 1995), and Ebola virus (Leroy, et al. 2004)) (Text Box 1).

There are limitations to our study, particularly ascertainment and reporting biases, as acknowledged in previous studies of EIDs (Woolhouse and Gowtage-Sequeria 2005, Jones, et al. 2008). In addition, differences in the number of species belonging to each order, the difficulty of testing inaccessible species and limits to reliable diagnoses of emerging viruses have an impact, especially in resource-poor settings. Further, many disease states are not recognizable in free-ranging mammalian species under field conditions. Lastly, there is a risk that an animal may be co-infected with a number of agents, only one of which causes disease; or that co-infection may have an additive or synergistic effect on clinical signs, and that anthropozoonotic viruses artificially inflate the 'disease' count of some mammalian orders over others. However, our findings are based on an aggregation of the best data available to date on host health as it relates to zoonotic viruses and have useful implications for public health.

Our analysis supports a holistic, probability-based approach to zoonotic virus discovery (Supporting Text Box 1), specifically, continued analysis of passively- and actively-reported mortality events and increased investment in broad surveillance of healthy wildlife. The latter could be targeted geographically to those regions most likely to generate novel EIDs (Jones, et al. 2008) or taxonomically to those groups which are reservoirs for the highest proportion of zoonoses (Woolhouse and Gowtage-Sequeria 2005, Cooper, et al. 2012). These efforts could be envisaged as part of a strategy for 'smart surveillance', heightening the opportunity for discovery of novel zoonoses, particularly if wildlife are sampled at key interfaces where contact with people or domestic animals and thus the opportunity for spillover is highest.

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Source	Award	Target	Comment
Emerging Pandemic Threats PREDICT program (PREDICT) < United States Agency for International Development (USAID) –		**Error! Reference source not found.**	Awarded to Peter Daszak, PhD

Source	Award	Target	Comment
Washington, D.C., USA			
National Institute of Allergy and Infectious Diseases (NIAID) – Bethesda, MD, USA	R01 AI079231 "Non-biodefense emerging infectious disease research opportunities award"	Peter Daszak, PhD	
Research and Policy for Infectious Disease Dynamics program (RAPIDD) < Science and Technology Directorate < U.S. Department of Homeland Security (DHS)		Dr. Tiffany L Bogich, PhD	
Fogarty International Center < National Institutes of Health (NIH) – Bethesda, MD, USA		EHA	
	3R01TW005869-06S1 "American Recovery and Reinvestment Act award (ARRA)"	The work	Awarded to Billy Karesh, DVM

Disclosures

The authors have read and understood the journal policy on declaration of interests and declare the following interests: Billy Karesh, DVM serves as president of Working Group on Wildlife Diseases at the World Animal Health Organization (OIE) in Paris, France.

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Supporting Information

Previous analyses show that zoonotic disease emergence events and human pathogen species richness are spatially correlated with mammal and bird diversity (Jones, et al. 2008). However, these studies weight all species equally. In reality, the risk of zoonotic viral transmission, or spillover, likely varies among host species due to differences in underlying viral richness, opportunity for contact with humans, propensity to exhibit clinical signs that exacerbate viral shedding, other ecological, behavioral and life-history differences, and phylogenetic distance from humans. We hypothesize that the number of viruses a given mammal species shares with humans decreases with phylogenetic distance from humans and increases with opportunity for human contact. We used generalized additive models (GAMs) to identify and rank host-specific

predictors (ecological, life history, taxonomic, and phylogenetic traits, and a control for research effort) of the number of total and zoonotic viruses in mammals.

Methods

Database

To construct the mammal–virus association database we initially extracted all viruses listed as occurring in any mammal from the International Committee on Taxonomy of Viruses database (ICTVdb), and further individually went through each virus listed in the ICTV 8th edition master list and searched the literature for mammalian hosts.

[data.xlsx]

Supporting Dataset 1 Database of all human emerging viruses previously identified as originating in wildlife. Data from: (Morse 1993).

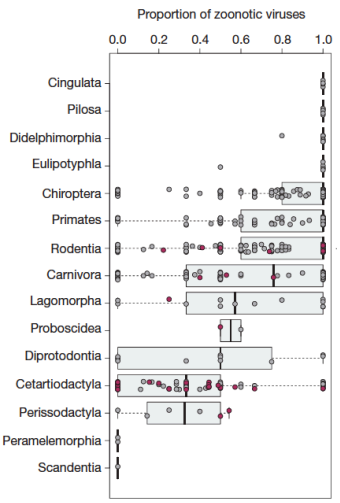
https://www.ncbi.nlm.nih.gov/nuccore/KJ501319

Supporting Dataset 2 West Nile Virus genome Data from: (Eidson, et al. 2001).

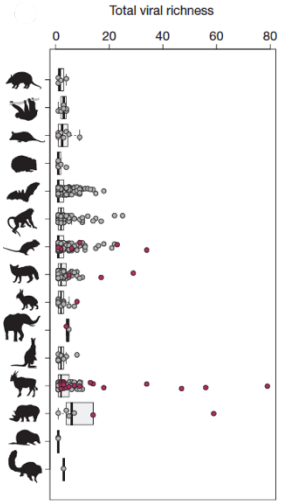
Supporting Code 1 Log helper function for model fitting.

```
logp = function(x){   # Fn to take log but make zeros less 10x less than min
 # x[is.na(x)] <- 0
 m = min(x[ x > 0], na.rm=T)
 x = log( x + m )
 return(x)
}
```

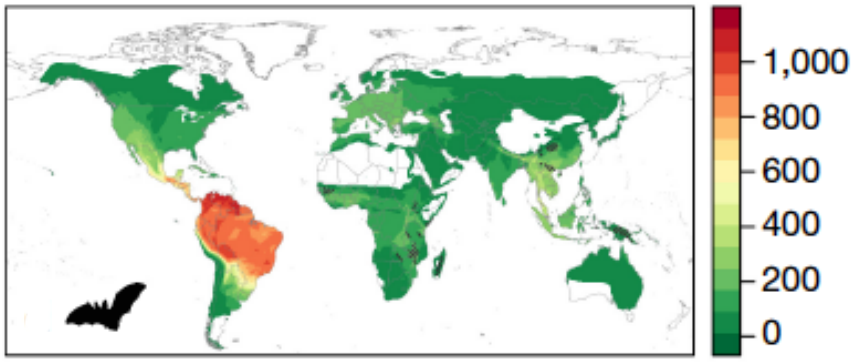
A



B



Supporting Figure 1 Observed viral richness in mammals. (A) Total viral richness per species. (B) Total virus richness aggregated by order. Code from: Supporting Code 1.



Supporting Figure 2 Chiroptera viral richness by location.

Supporting Table 1 Summary of best fit model for total viral richness (all data, n=576 species). Data from: Supporting Dataset 2.

Term	Chi-sq statistic	p-value
Disease-related publications (log)	1846.57	<0.001
Mammal sympatry (>20% range overlap)	301.38	<0.001
Order CHIROPTERA	155.12	<0.001
Order RODENTIA	95.49	<0.001
Order PRIMATES	34.4	<0.001

Supporting Text Box 1 Additional summary of results. Author: Prof. Christine Kreuder Johnson, DVM, MPVM, PhD.

The analyses reported herein have broad potential to assist in expediting viral discovery programs for public health. Our host-specific analyses and estimates of missing zoonoses allow us to identify which species and regions should be preferentially targeted to characterize the global mammalian virome. Our viral trait framework then allows prioritization of newly discovered wildlife viruses for detailed characterization (for example, by sequencing receptor-binding domains, and conducting in vitro and in vivo infection experiments (Taylor, Latham and Woolhouse 2001)) to assess their potential to threaten human health.

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