

Macroevolution of virulence shifts in human-infective RNA virus species

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Declaration

All data analyses described in this work and the written presentation of this thesis are my own work. This work builds on data collected by previous members of the Epidemiology Research Group at The University of Edinburgh (most notably by Dr. Feifei Zhang and Dr. Liam Brierley) and a methodology developed by Dr. Lu Lu. I was also supported in data collection by summer intern Miranda Ferguson. No part of the work herein has been submitted for consideration for any other degree or professional qualification.



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Finally, I would like to thank the members of the Epidemiology Research Group at The University of Edinburgh and the members of my committee Dr. Samantha Lycett, Prof. Andrew Leigh-Brown and Prof. Mark Woolhouse for interesting discussions and their feedback which improved this work.

Lay Summary

It is estimated that there are more viruses than stars in the universe, however not all viruses are capable of infecting humans. A particular category of viruses, called RNA viruses, are of special interest to human health due to their propensity to be zoonotic. Zoonotic viruses are viruses that can jump from animals to humans and well-known examples are SARS-CoV-2 and Ebola virus. Because of their importance to human health, efforts have been undertaken to monitor and understand the characteristics of these viruses. Currently, there are 263 documented human-infective RNA virus species. This is a diverse group of viruses known to infect many different hosts. They also range widely in their ability to cause disease in humans; some viruses can be fatal, whereas other viruses are benign such as the common cold. The severity of illness caused by a virus is called virulence.

The virulence of a virus can be studied in different ways and in this study, virulence is studied from an evolutionary viewpoint. Virulence is an evolvable trait, meaning that this trait can change over time. The way a trait evolves can be depicted in a similar way speciation is depicted: using a phylogenetic tree. A phylogenetic tree is a visual abstraction of the evolutionary process and is commonly used to visualize how different species have evolved from a common ancestor. Viruses can evolve to be more severe, or less severe depending on a variety of factors and this study has looked at how frequently and in which direction this has happened over deep evolutionary time.

Viruses are categorized as being either severe, moderate, non-severe or as not being able to infect humans and the evolutionary changes over time in these virulence categories are visualized on phylogenetic trees. By studying the phylogenetic trees, this study finds that most severe virus species in humans are likely to have directly evolved from viruses that are not capable of infecting humans. Moreover, non-severe viruses rarely evolve to become more severe in humans when they already have the ability to infect humans.

Altogether, this study provides an evolutionary dimension to a broader framework of studies that attempts to understand the variation in human disease severity of RNA

viruses upon human-infection. The findings from this study suggest that, from a macroevolutionary viewpoint, large virulence shifts are infrequent once RNA virus species have evolved human-infectivity.

Abstract

Study Objectives: To determine the frequency and distribution of virulence shifts across 40 viral genera that include human-infective RNA virus species using evolutionary discrete trait models.

Methods: An inhouse database containing RNA-dependent RNA polymerase (RdRp) gene sequences from human and non-human infective RNA virus species was updated in January – March 2021. RdRp gene sequences were obtained from NCBI GenBank for newly identified virus species. Data describing viral virulence in humans was obtained by a literature search in June 2021 and virus species were categorized as either being non-human-infective, non-severe, moderate or severe. Phylogenetic trees based on the RdRp gene sequences were estimated, discrete virulence trait evolution modelled, and discrete virulence trait transitions counted.

Results: The final dataset contained RdRp gene sequences of 579 viral species. 38.3% (222) of all viruses were human-infective of which 21.6% (48) were classified as severe, 11.7% (26) as moderate and 66.7% (148) as non-severe. The *Flavivirus* genus had the highest number of severe virus species (10). 83% of severe virus species or clades were likely to have evolved from non-human-infective ancestral viruses. Large virulence increases once a virus had evolved the ability to infect humans were rare as only 2 transitions from non-severe to severe were observed. Discrete trait transitions from severe to non-severe were more frequent with 10 transitions. Transition to moderate from non-severe or severe were more balanced with evidence of 8 and 4 transitions, respectively. When transitions from non-human-infective viruses to any virulence class were stratified by envelope, genome and transmission mode, no transitions to severe were found for non-enveloped, dsRNA and vector-borne viruses.

Conclusion: This study fits within a broader framework of comparative studies that attempts to understand the variation in virulence of viral genera that contain human-infective RNA viruses. The findings from this study suggest that, from a macroevolutionary viewpoint, the evolution of large virulence transitions are infrequent once RNA virus species have evolved human-infectivity.

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Introduction

Documenting viral diversity

Mammalian viral diversity is not well characterised and estimates of the total number of virus species range from 1.6 million to a more conservative 40,000 depending on which estimation method is used (Carlson et al., 2019; Carroll et al., 2018). Considering only zoonotic viruses, i.e. viruses that can be transmitted from animals to humans, these estimates are lower and range from 500,000 to 10,000. This latter diversity estimate comprises approximately 4,000 DNA and 6,000 RNA viruses reiterating the notion that RNA viruses are more likely to be zoonotic compared to DNA viruses (Carlson et al., 2019; Carroll et al., 2018).

The number of documented, rather than estimated, human-infective RNA virus species is a fraction of the above estimates. Considering only RNA virus species recognised by The International Committee on Taxonomy of Viruses (ICTV), as of September 2021, the total number of documented human-infective RNA virus species is 263, spanning 60 genera and 23 families (updated version of Woolhouse and Brierley, 2018). This number has gradually increased over time, with 180 known human-infective RNA virus species reported in 2013, 214 in 2018, and 223 in 2020 (Woolhouse et al., 2013; Woolhouse and Brierley, 2018; Zhang et al., 2020). This increase reflects true new viral discoveries, e.g. the discovery of *Tacheng uukuvirus* in China in 2019 (Dong et al., 2021), however it also reflects continuous changes in viral taxonomy driven partly by the increased availability of viral genomic data allowing for better species delineation using phylogenetics compared to serotype delineation (Gorbalenya et al., 2020; Walker et al., 2022). For example, *Hepatitis delta virus* used to be the only species in the *Deltavirus* genus, however it was split up into 8 distinct species in 2021, namely: *Deltavirus cameroonense*, *Deltavirus carense*, *Deltavirus italiense*, *Deltavirus japanense*, *Deltavirus peruense*, *Deltavirus senegalense*, *Deltavirus taiwanense* and *Deltavirus togense* (Walker et al., 2021).

Introducing comparative research into RNA viruses

Documenting human-infective RNA virus species does not only provide insights into how many viruses might exist, but it has also incentivised a comparative research theme aimed at understanding commonalities of successful human RNA viruses. For

example, by comparing 203 virus species that can infect humans and their characteristics such as transmission mode and genomic architecture, Geoghegan et al. (2016) found that non-segmented, non-vector borne, non-enveloped viruses with low host mortality had the highest likelihood of being transmissible in humans. Similarly, Zhang et al. (2020) collected information on the geographical discovery location of 223 human RNA viruses and subsequently modelled these locations to create a world map with probabilistic hotspots for viral discovery. The rationale connecting these studies is that comparative data can help identify trends which may not be evident from studying case studies in isolation. Information from these trends, may it be risk factors of human-transmissibility or disease discovery hotspots, may then prove useful during risk assessment for unknown viruses or may help guide disease surveillance efforts.

Comparative research has thus given us more a detailed understanding of successful human RNA viruses, yet two viral traits are incontrovertibly important to human health: human transmissibility and virulence (Woolhouse et al., 2016). Human transmissibility relates to a virus's ability to spread in a human population, either directly from person-to-person or indirectly through mediators such biological vectors or the environment (Lloyd-Smith et al., 2009). A virus's transmission potential can be expressed in terms of its basic reproduction number (R_0), i.e. the average number of infected contacts per infected individual in a totally susceptible population. Introduction of viruses with a $R_0 < 1$ result in self-limiting outbreaks, whereas introduction of viruses with a $R_0 > 1$ can lead to large scale epidemics if not curtailed (Lloyd-Smith et al., 2009).

Viral virulence relates to the severity or harmfulness of a virus and will be the central theme of this study. Human infective RNA virus species display large natural variation in virulence upon human infection. For example, *Zaire ebolavirus* has a case fatality ratio in the 80% range, whereas another species in the same viral genus, *Reston ebolavirus*, has not been associated with human disease (Van Kerkhove et al., 2015; Miranda et al., 1999). Documenting this variation is important and understanding why some viruses cause more severe disease in humans than others is a major research area that has been studied from various angles (Cressler et al., 2015). Typical biomedical studies investigate the molecular and immunological determinants of disease severity in a particular host for a single virus species. Alternatively, theoretical

work studies viral virulence using mathematical models and evolutionary theory (Alizon et al., 2009). At the heart of this theoretical approach are mathematical models that formalise the relationship between a virus's fitness (its basic reproductive number R_0), and parameters such as transmission rate, density of susceptible hosts and mortality due to infection (i.e. its virulence). How virulent a virus will evolve is then determined by its unique life-history traits (Cressler et al., 2015; Day, 2002).

Comparative research has also explored the variation in disease severity of RNA viruses. For example, by fitting random forest models on comparative trait data of 214 human infective RNA viruses, Brierley et al. (2019) found that notable predictors for RNA viruses to cause severe disease in humans are having neural and/or renal tissue tropism, direct or respiratory transmission routes, and limited human-to-human transmissibility. Similarly, by studying 345 directly transmitted mammalian viruses Guth et al. (2019) found that hosts that are phylogenetically more closely related to humans harbour zoonotic RNA viruses of lower impact in terms of morbidity and mortality, whereas more distantly related hosts harbour more virulent zoonotic RNA viruses.

Virulence in a phylogenetic framework

In this study, the comparative research theme into RNA virus virulence in humans is expanded with an evolutionary dimension. Using a phylogenetic framework, the evolution of viral virulence is studied across many viral genera. Phylogenetics refers to the study of evolutionary relationships among species (Felsenstein, 2004). This relationship can be inferred from genetic sequence data and subsequently depicted with a phylogenetic tree. Once a phylogenetic tree is inferred, the evolution of traits can be modelled using evolutionary trait models (Harmon, 2019; Harvey and Pagel 1991). The simplest of these models for discrete traits, the Mk model, assumes that transitions from one trait state to another follow a Markov process and that transition rates between all possible states are equal (Pagel, 1994; Lewis, 2001). This model may be extended by allowing asymmetric rates. Such a model can then be fit to comparative trait data and a phylogenetic tree, allowing for probability estimates of ancestral states of internal nodes in the phylogenetic tree. By defining virulence as the average disease severity upon infection in healthy humans and by discretizing it in for example “non-severe” (e.g. mild and/or asymptomatic infections), “moderate” (e.g.

generally mild infections, however with the occasional severe case) and “severe” (e.g. severe infections associated with significant morbidity and mortality), discrete trait transitions, i.e. virulence shifts, can be detected on the tree and key branches of interest detected.

By using such a comparative phylogenetic framework, one could now ask broad questions such as: do viruses causing severe disease in humans mainly evolve from other related viruses known to cause severe disease in humans and is this trait mainly determined by the viral genus? And how does viral virulence in humans evolve after a virus gains the ability to infect humans? The latter is a central question in the study of disease emergence, however comparative studies that examine how the existing variation in RNA virus human disease severity might have evolved are lacking (Geoghegan and Holmes, 2018). Empirical evidence indicates that viral virulence can evolve in a relatively short period of time. The epidemiology of West Nile virus (WNV) provides an intriguing example as WNV evolved to become more virulent within less than a decade. WNV is a mosquito-borne virus and infects birds and mammals including humans and horses. It was first isolated in the West Nile district of Uganda in 1937 from a febrile patient (Smithburn et al., 1940) and prior to 1996 WNV had only been associated with mild febrile infections in humans (Brault et al., 2007). From 1996 onwards, the incidence of viral encephalitis caused by WNV in humans increased in various geographical locations around the world (Hayes et al., 2005). For example, in the United States 69 neuroinvasive cases of WNV were reported in 1999 which increased to 2,866 in 2003 (Hayes et al., 2005). Widespread mortality of bird species was also observed, especially in the abundant American crow (*Corvus brachyrhynchos*). Phylogenetic analysis on WNV genomes isolated from birds at multiple geographical locations revealed that a single threonine to proline amino acid substitution at position 249 in the NS3 helicase protein (NS3-T249P) was associated with the high virulence phenotype. These results were later corroborated by *in vivo* experiments, which showed an increased rate of virus replication and subsequent viraemia of the NS3-T249P mutant in the American crow compared to wildtype (Brault et al., 2007).

Study aims

This study aims to determine the frequency and distribution of evolutionary virulence shifts across 40 viral genera that include human-infective RNA virus species. To do this, a dataset containing amino acid sequences from 579 human and non-human infective non-reverse transcribing (RT) RNA virus species isolated from mammals and birds is compiled and analysed. This dataset covers 84% (222/263) of the total number of known human-infective RNA virus species and 67% (40/60) of all known viral genera containing human-infective RNA virus species (updated inhouse version of Woolhouse and Brierley, 2018). Using primary epidemiological data on case fatality ratio and clinical disease manifestation, each viral species is assigned a virulence level and classified as either being “severe”, “moderate”, “non-severe” or not being able to infect humans (“no-human-disease”). Discrete trait models are then fitted to comparative virulence data and phylogenetic trees. Trees with reconstructed ancestral virulence states are then examined for evidence of virulence shifts over deep evolutionary time.

Methods

Data Collection

Polymerase gene sequences data

A database containing RNA dependent RNA polymerase (RdRp) gene sequences for viral species from genera known to contain human-infective non-RT RNA virus species was obtained from Lu et al. (2019). In March 2021, a search was conducted to identify new viral sequences that could be added to this database. For this search, the ICTV 2019.v1 master species list (MSL) was downloaded and viral species in this list were compared to the database of Lu et al. (2019) and an updated version of our inhouse human-infective RNA virus species database (Woolhouse and Brierley, 2018; Zhang et al., 2020). NCBI GenBank queries were then performed for virus species that were not present in Lu et al. (2019) but were in the ICTV 2019.v1 MSL and our inhouse database. Inclusion criteria were that complete or nearly complete polymerase gene sequences were available, together with information on which host the virus was isolated from. Given the primary interest of this study in virulence shifts after a virus is inferred to have gained human-infectivity, only viral sequences isolated from mammal and birds were included. This was done to reflect that most known zoonotic pathogens have mammals and birds as their natural host (Woolhouse et al., 2012). An exception to this host inclusion criterium was made for confirmed human-infective RNA virus species that only had sequences available from their natural vectors. *Nyando orthobunyavirus*, for instance, is a human-infective virus species first described in 1965 (Williams et al., 1965) and it has one only one complete sequence available isolated from its arthropod vector (Groseth et al., 2014). The availability of genome sequences also varies greatly between virus species. For example, as of January 2023, the number of genome sequences available for virus species with a high incidence of human disease within the *Flavivirus* genus range from 2,000 for *Yellow Fever virus* to 40,000 for *Dengue virus* (Brister et al., 2015). Contrarily, there is only one genome sequence available for *Uganda S virus*; a rare species within the *Flavivirus* genus (Grard et al., 2010). To deal with this range of genome availability, a selection of five sequences per host species per virus was included in the database if there were multiple polymerase sequences available for a virus species. Care was

taken not to include sequences that were submitted to NCBI from the same outbreak and/or geographical location.

The updated database contained 1941 RdRp gene sequences, spanning 579 viral species and 40 genera. Fourteen virus genera containing human-infective virus species were not included in the final data set. Either because the genus only consists of one virus species (e.g. *Tanzavirus*) or no sequences satisfied the eligibility criteria. These excluded genera are: *Thottimivirus*, *Uukuvirus*, *Bandavirus*, *Seadornavirus*, *Recovirus*, *Rubivirus*, *Tanzavirus*, *Coltivirus*, *Erbovirus*, *Marburgvirus*, *Seadornavirus*, *Thogotovirus*, *Tibrovirus*, *Torovirus*, *Deltavirus*, *Rubivirus* and *Salivirus*. *Retroviridae* and *Influenza A* genus were also excluded a priori given their markedly different biology compared to the other RNA viruses in the dataset as per Lu et al. (2019).

Disease severity data

RNA virus species were classified into four virulence categories: “severe”, “moderate”, “non-severe” and not being able to infect humans (“no-human-disease”). Following Brierley et al. (2019), these four categories aim to capture broad variation in human disease severity upon infection apparent from epidemiological data. Given that disease severity is a function of both human and virus traits, mortality in healthy adults is taken as our baseline. Implicit in the four virulence categories is the association of a virus species with mortality in healthy adults compared to vulnerable individuals (defined below).

1. Viruses were classified as “severe” if they had >5% Case Fatality Ratio (CFR), reports of hospitalisation, were associated with significant morbidity from certain conditions (e.g. haemorrhagic fever, seizures/coma, cirrhosis, hantavirus pulmonary syndrome) or were explicitly described as severe or causing severe disease.
2. Viruses were classified as “moderate” if they did not fit the severe criteria, however have been reported to have caused fatalities in healthy adults or contain severe strains or subspecies to have caused fatalities in healthy adults.
3. Viruses were classified as “non-severe” if they had never been reported to cause fatalities in healthy adults or only have been reported to cause fatalities

in vulnerable individuals (which are defined as being age 16 or below, or age 50 and above, immunosuppressed or having comorbidities).

4. Viruses were classified as “no-human-disease” if a virus species is not currently known to infect humans.

Data used to classify viruses was obtained from data published by Brierley et al. (2019) and from a literature search conducted in June 2021.

Human-infective RNA virus species data

A literature search was conducted according to a protocol by Woolhouse and Brierley (2018) in order to identify newly identified human-infective RNA viruses that were not present in Zhang et al. (2020). 41 new species of human-infective viruses were found, although many of these were not newly discovered species but were split from previously known viral species based on phylogenetic demarcation. An overview of the newly discovered human-infective RNA virus species is shown in **Supplementary Table 3**, bringing the total number of documented ICTV-recognized human-infective RNA virus species to 263.

Phylogenetic analysis

Phylogenetic analyses were performed using the Bayesian Evolutionary Analysis Sampling Trees (BEAST) 1 software package (v.1.10.4) (Suchard et al., 2018). Amino acid polymerase sequences were aligned for each virus genus with MAFFT (v7.475) using the accuracy-orientated method L-INS-I (Kato and Standley, 2013). Phylogenetic trees were estimated using the aligned amino acid polymerase sequences with the Markov chain Monte Carlo (MCMC) method in BEAST. Based on previous analyses, a WAG model with a gamma distribution across sites was chosen as the substitution model with an uncorrelated log-normal relaxed molecular clock model (Lu et al., 2019). Depending on the viral genus, a constant size coalescent tree prior or a Yule process prior was chosen. The decision for tree prior was made based on composition of sequences in each viral genus. If sequences were mainly from different viral species, then a Yule process prior was chosen, whereas if multiple sequences of the same viral species were present in the genus, then a coalescent tree prior was chosen. Branch lengths were scaled by substitution rate per site. The

chain was set to 100 million iterations and trees were sampled every 10,000 iterations. This resulted in a posterior sample of 10,000 trees for each virus genus.

For discrete trait analyses, a sample of 1,000 trees was obtained from the original posterior sample of 10,000 trees. Each sequence was assigned a virulence category and an asymmetric discrete trait model was fit on this sample of 1,000 trees. The Markov chain was set to 1,100,000, burn-in set to 10% and trees were sampled every 10,000 iterations. Summary Maximum Clade Credibility (MCC) trees were created using TreeAnnoter software. The disease-severity state was inferred at the root node. Transitions in disease severity were defined as a change in the most probable discrete trait between any two adjacent nodes on the phylogeny. The number of transitions were counted by visually examining the phylogenies with mapped ancestral virulence traits and by subsequently comparing counts to the mean number of trait changes, i.e. Markov Jumps, that were estimated in BEAST (Minin and Suchard, 2008).

Statistical Analyses

Odds ratios and their 95% confidence intervals quantifying the relationship between human-infectivity of the ancestral parent node and subsequent virulence shift were estimates using Fisher's exact test. All analyses were performed using R statistical software (version 4.2.1).

Computational resources

This work has made use of the Linux Compute Cluster (Eddie) provided by the Edinburgh Compute and Data Facility ([ECDF](#)).

Results

The final dataset included 579 RNA virus species of which 8.3% (48) were classified as severe, 4.5% (26) as moderate, 25.6% (148) as non-severe and 61.6% (357) as no-human-disease. An overview of the number of viral species (n=579) stratified by viral genus (n=40) and their associated virulence categories is shown in **Figure 1**.

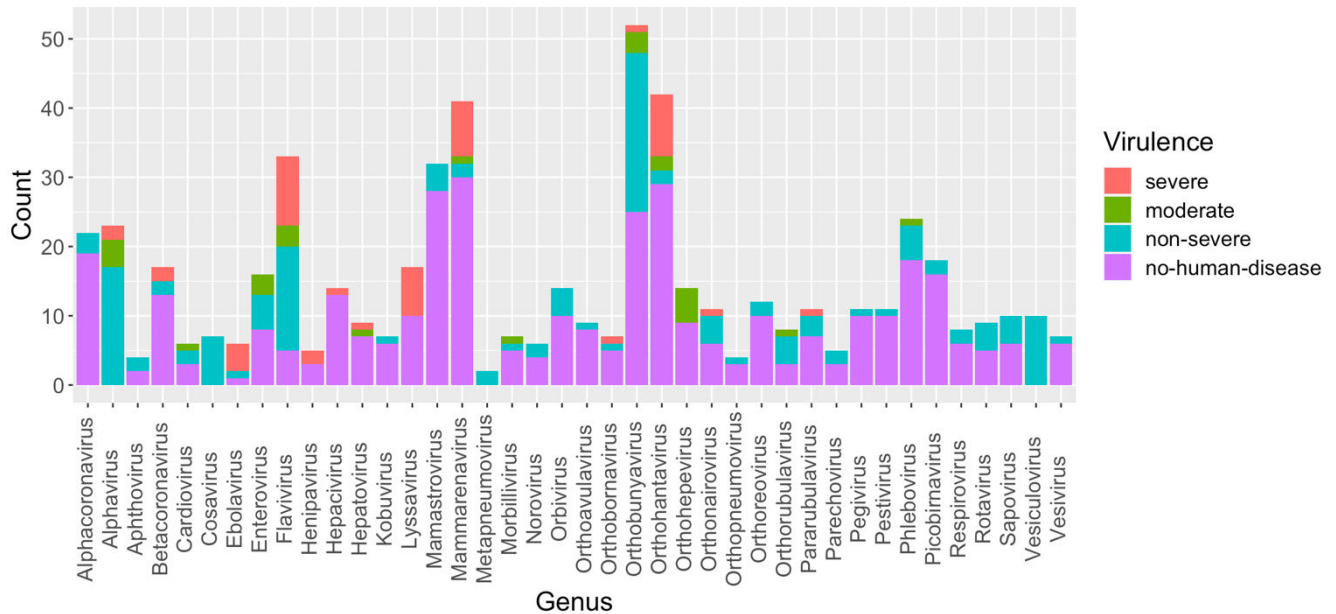


Figure 1: Bar plot showing the number of viral species in the dataset stratified by viral genus. Viruses were classified as severe, moderate, non-severe and no-human-disease.

Severe viruses were found in 35% (14/40) of viral genera, whereas moderate and non-severe viruses were found in 30% (12/40) and 88% (35/40) of genera respectively. The *Flavivirus* genus had the highest number of severe virus species (10) although the *Ebolavirus* genus had the highest proportion of severe virus species (67%) and *Orthobunyavirus* genus the lowest (1.9%). Proportions of severe viruses were not equally distributed across viral genera (Fisher's exact, 1000 simulations, $p < 0.001$).

Phylogenetic analysis

Bayesian phylogenetic trees for each viral genus were inferred and discrete trait models were fit using the phylogenetic trees and comparative virulence trait data. This resulted in phylogenetic trees with the most probable virulence discrete state mapped onto each node. Phylogenetic trees for all viral genera are shown in **Figures 2-4**.

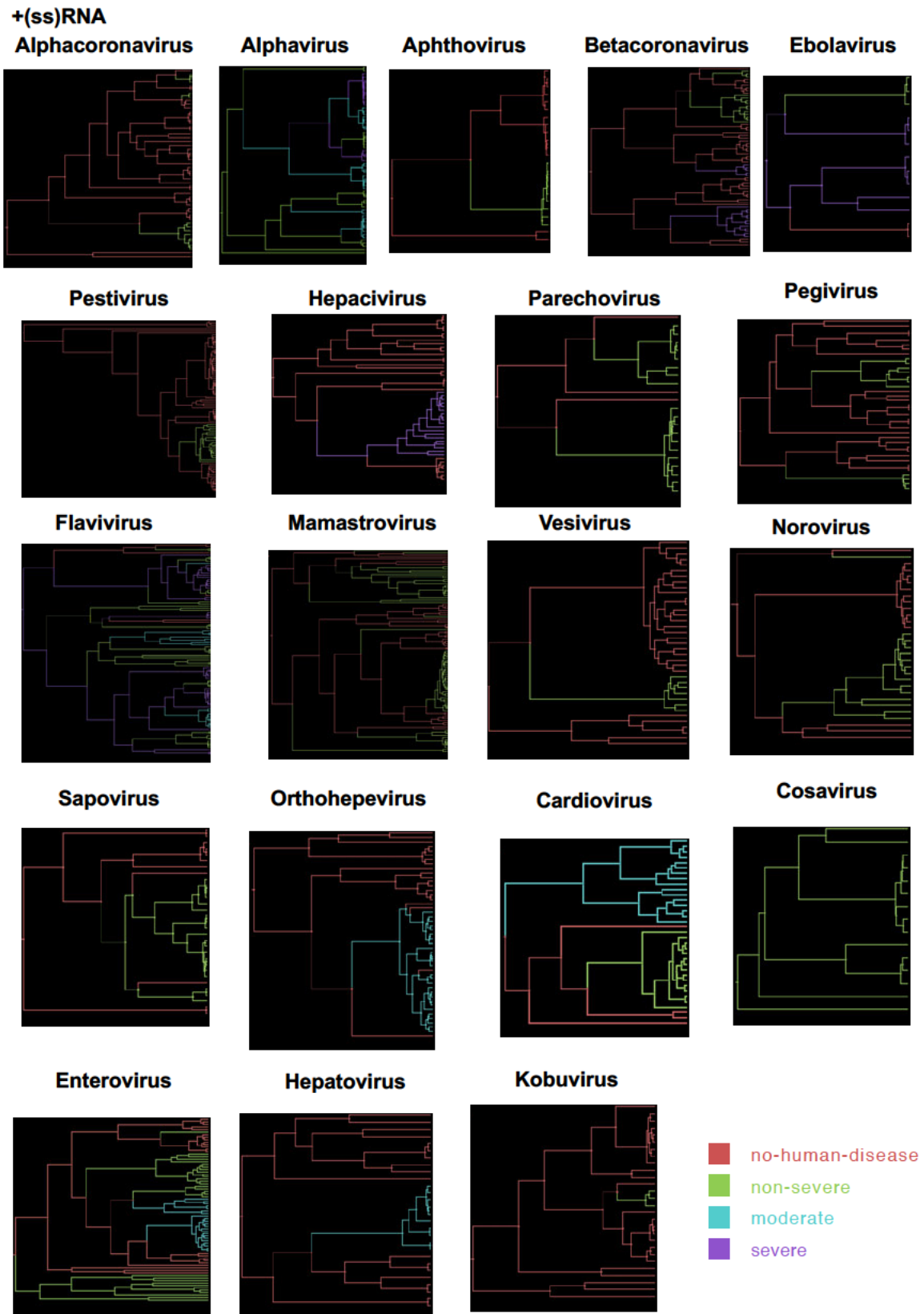


Figure 2: Bayesian maximum clade credibility (MCC) phylogenetic trees of +(ss)RNA viral genera. The MCC trees show the most probable transitions between viruses not able to infect humans (no-human-disease) in red, those causing non-severe disease (green), moderate disease (blue) and severe disease (purple). Tip labels are not shown. Scale bar indicates amino acid substitutions per site. Phylogenies were constructed using RdRp amino acid sequences.

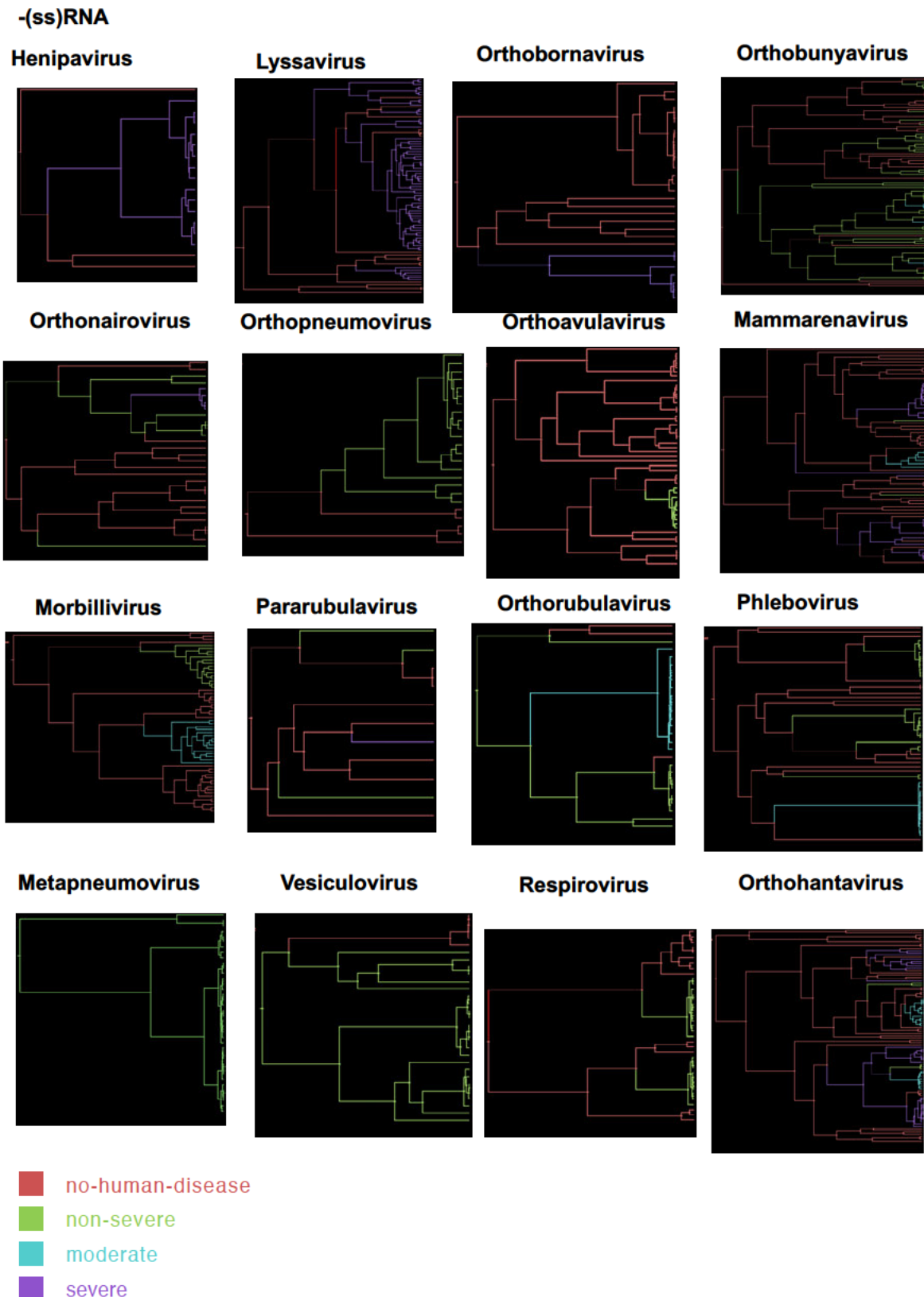


Figure 3: Bayesian maximum clade credibility (MCC) phylogenetic trees of -(ss)RNA viral genera. The MCC trees show the most probable transitions between viruses not able to infect humans (no-human-disease) in red, those causing non-severe disease (green), moderate disease (blue) and severe disease (purple). Tip labels are not shown. Scale bar indicates amino acid substitutions per site. Phylogenies were constructed using RdRp amino acid sequences.

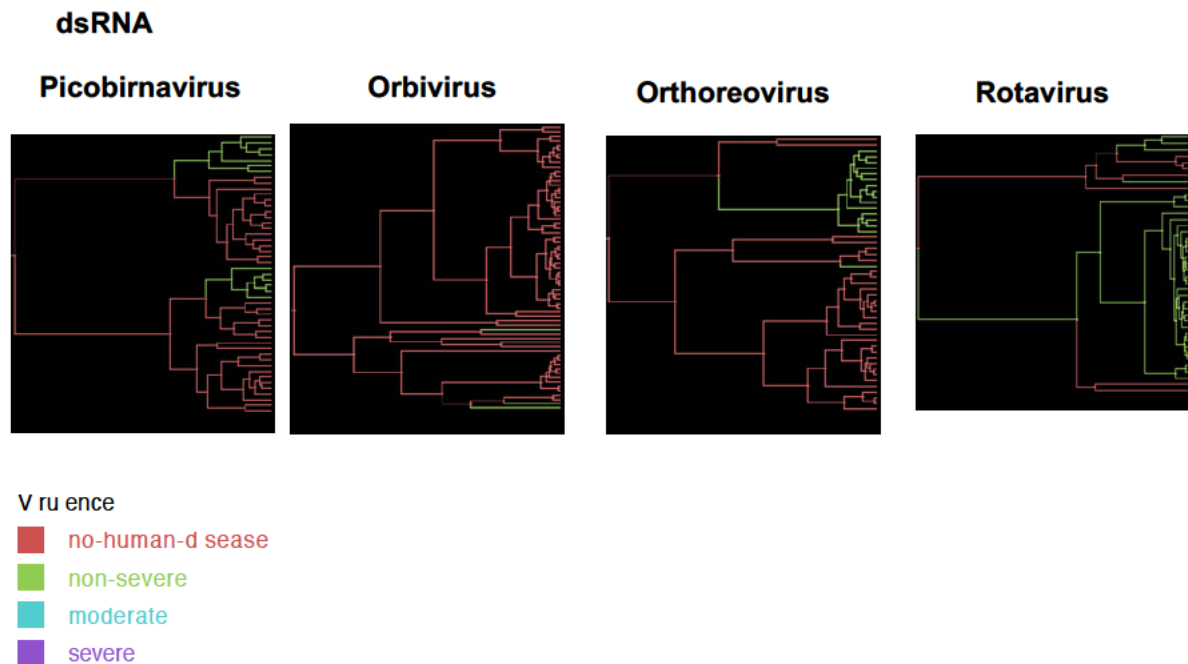


Figure 4: Bayesian maximum clade credibility (MCC) phylogenetic trees of dsRNA viral genera. The MCC trees show the most probable transitions between viruses not able to infect humans (no-human-disease) in red, those causing non-severe disease (green), moderate disease (blue) and severe disease (purple). Tip labels are not shown. Scale bar indicates amino acid substitutions per site. Phylogenies were constructed using RdRp amino acid sequences.

Ancestral state at root node

For each phylogenetic tree, the most probable ancestral state at the root node was inferred (**Supplementary Table 2**). The most probable ancestral state at the root node was “no-human-disease” for 80% (32/40) of genera. These results suggest that human-infectivity is not likely to be an ancestral trait for the majority of viral genera in the dataset as the “no human-disease” trait label is a proxy for “not known to be able to infect humans”. “Non-severe” was the most probable ancestral trait label at the root node for 15% (6/40) of genera (*Alphavirus*, *Aphovirus*, *Cosavirus*, *Orthorubulavirus*, *Vesiculovirus* and *Metapneumovirus*) and “severe” for 5% (2/40) of genera (*Ebolavirus* and *Flavivirus*). No genus had “moderate” as their inferred ancestral root node state.

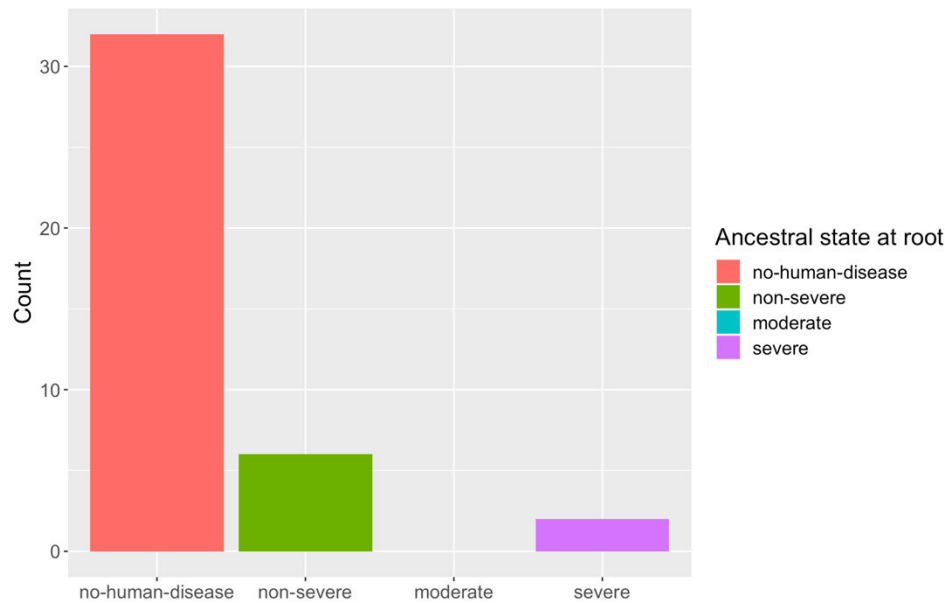


Figure 5: Bar plot showing the distribution of most probable ancestral root state for all genera. 32 genera had “no-human-disease” as their most probable state, 6 “non-severe”, 2 “severe” and none were “moderate”.

State Transitions

Transitions to severe

The phylogenies were examined for discrete trait transitions, and firstly, transitions from any virulence class to the severe class were examined. For each genus-level phylogeny, the number of transitions were counted. Transitions were defined as a change in the most probable virulence state between a parent and child node. Across all 40 viral genera, 19 transitions from no-human-disease to severe were counted whereas only 2 transitions from non-severe to severe and 2 transitions from moderate to severe were counted (**Figure 6** and **Table 1**). These results imply that non-severe and moderate viruses are not likely to evolve to become more severe in humans and that most severe (83%) viruses and clades are likely to have evolved from ancestral viruses not able to infect humans. Additionally, each viral genus is characterised by a single discrete trait transition type.

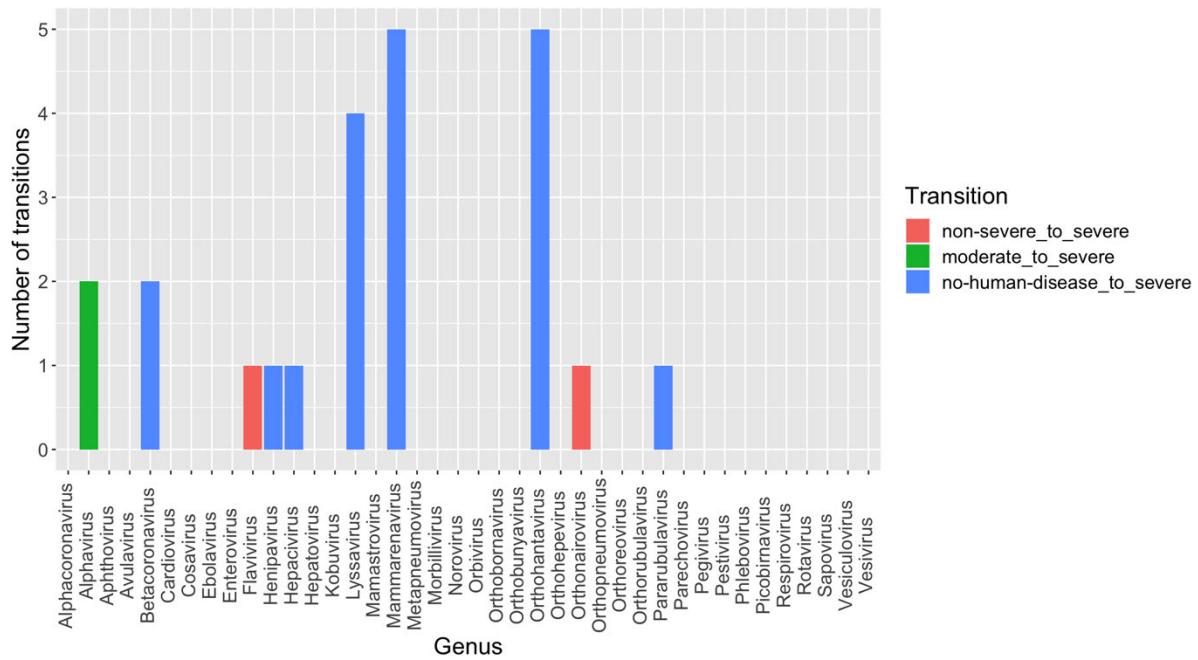


Figure 6: Bar plot showing the number of forward transitions to the severe class for each viral genus.

The genera in which evidence was found for forward transitions from non-severe to severe were further examined. These transitions were found in the *Flavivirus* and *Orthonairovirus* genus; both of which are characterised by a vector-borne transmission mode. **Figure 7** shows the two phylogenies and reveals that the severe virus species *Yellow Fever virus* and the *Crimean-Congo hemorrhagic fever orthonairovirus* evolved from a human-infective non-severe ancestor within a non-severe clade. The relevant transitions are marked by a red asterisk.

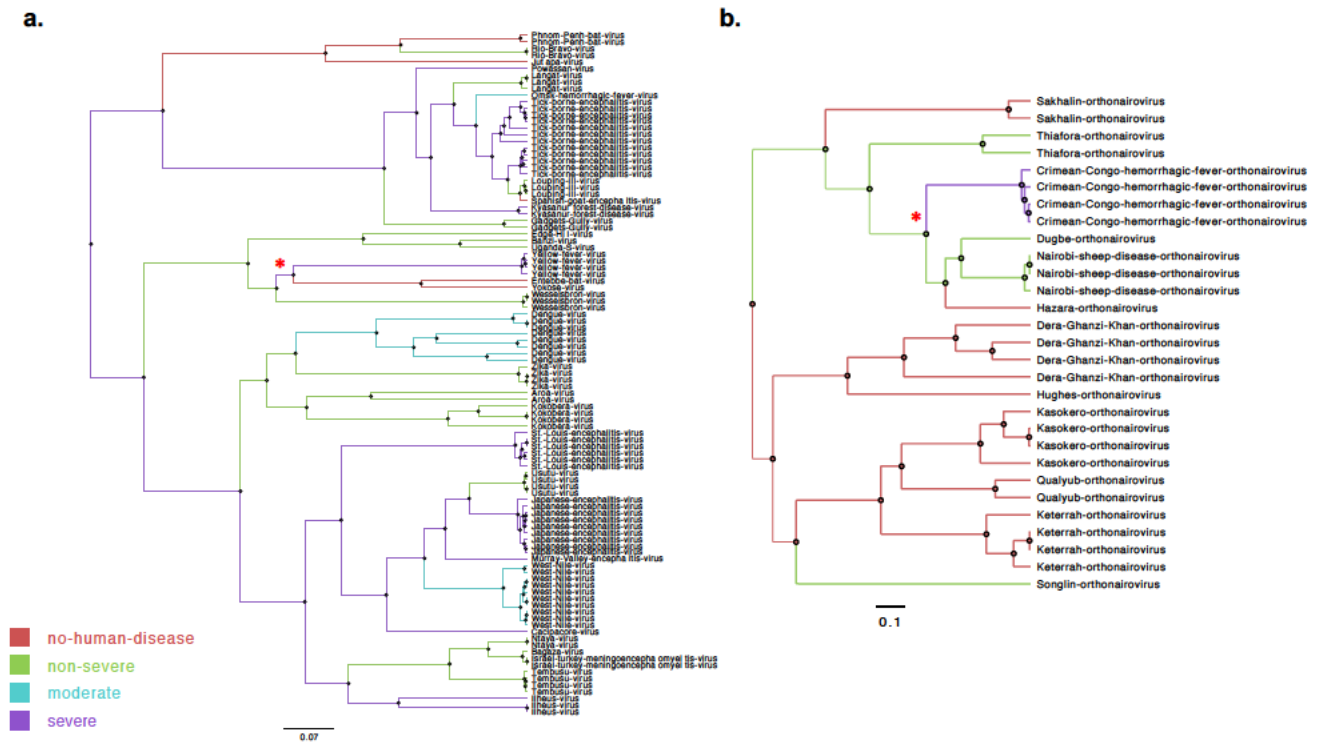


Figure 7: Maximum clade credibility (MCC) trees for the genera in which evidence was found for forward transitions from non-severe to severe. (a). MCC tree of the *Flavivirus* genus. (b). MCC tree of the *Orthonairovirus* genus. Scale bar indicates amino acid substitutions per site. Phylogenies were constructed using RdRp amino acid sequences.

Transitions to non-severe

Transitions from any virulence class to non-severe were next examined (**Figure 8**). Ten transitions were counted from severe to non-severe, although 80% (8/10) of these were in the *Flavivirus* genus. The ancestral root state of the *Flavivirus* genus was inferred to be severe therefore any non-severe clades or species will have evolved from a severe ancestor, inflating the severe to non-severe count (**Figure 7a**).

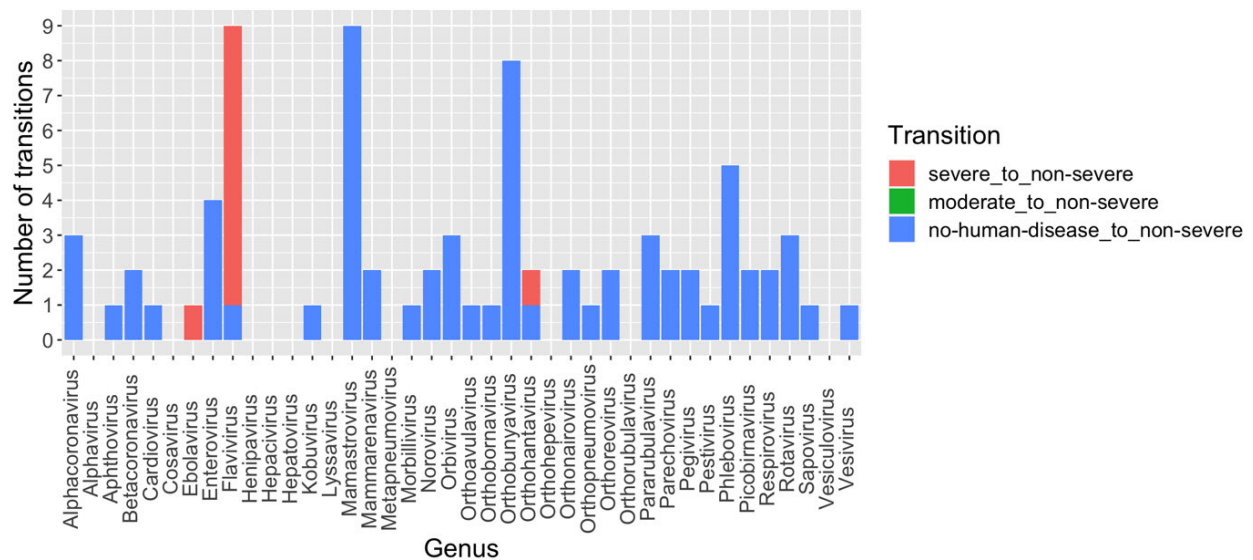


Figure 8: Bar plot showing the number of forward transitions to the non-severe class for each viral genus.

The other two severe to non-severe transitions were found in the *Orthohantavirus* genus and the *Ebolavirus* genus. The phylogenies for these two genera are shown in **Figure 9**. The red asterisks mark the relevant transitions. *Thailand orthohantavirus* and *Reston ebolavirus* both evolved within severe, human-infective viral clades.

Transitions to moderate

Transitions were also examined from any virulence class to moderate. In total, 9 transitions were counted from no-human-disease to moderate, 8 transitions from non-severe to moderate and 4 from severe to moderate. Similar to the severe to non-severe transitions, 50% (2/4) of these were found in the *Flavivirus* genus. The phylogenies of the *Alphavirus* genus and the *Orthobunyavirus* genus were further examined (**Figure 11**).

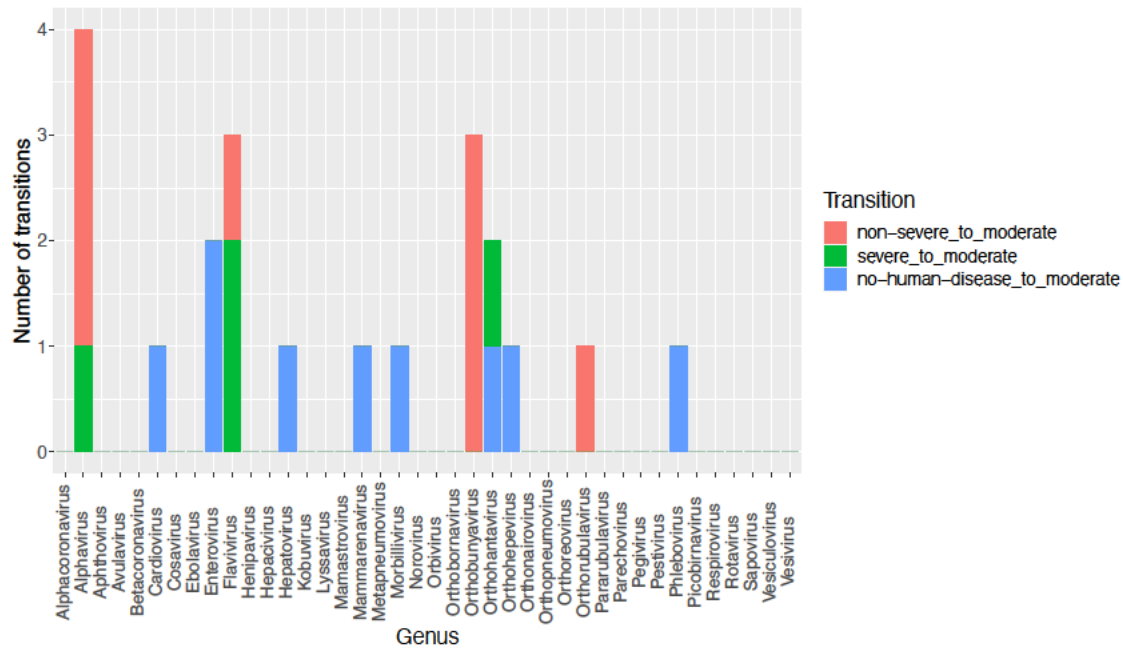


Figure 10: Bar plot showing the number of forward transitions to the moderate class for each viral genus.

The phylogenies of the *Orthobunyavirus* genus (**Figure 11a**) show convergent evolution of 3 moderate species from a non-severe clade. The *Alphavirus* genus (**Figure 11b**) shows a mixed virulence viral clade arising from a non-severe ancestor and two convergent events from non-severe to moderate in another clade. The relevant transitions are marked by a red asterisk.

Lastly, transitions from no-human-disease to any virulence class were examined. This can be interpreted as the most likely change in virulence class after a virus is inferred to have evolved human-infectivity. There were 68 transitions from no-human-disease to non-severe, 9 to moderate and 19 to severe (**Figure 12**).



Figure 3 consists of three stacked bar charts. The y-axis for all charts is 'Proportion of total transitions' ranging from 0.0 to 0.6 or 0.8. The x-axis categories are Envelope, Genome, and Transmission Route. The legend indicates three transition types: no-human-disease_to_severe (red), no-human-disease_to_moderate (green), and no-human-disease_to_non-severe (blue).

Category	Transition Type	Proportion of total transitions
Envelope	no-human-disease_to_severe	0.20
	no-human-disease_to_moderate	0.05
	no-human-disease_to_non-severe	0.30
Genome	no-human-disease_to_severe	0.15
	no-human-disease_to_moderate	0.05
	no-human-disease_to_non-severe	0.32
Transmission Route	no-human-disease_to_severe	0.18
	no-human-disease_to_moderate	0.05
	no-human-disease_to_non-severe	0.55

30

Summary of all transitions

Transition counts for all examined transition types are summarised in **Table 1**.

Table 1: Number and percentage of discrete trait transitions across all viral genera (n=40). The arrow '->' indicates the direction of the transitions from the parent node to the child node in the phylogenetic tree.

Type of transitions	Count	Percentage (%)
Forward to severe		
no-human-disease -> severe	19	82.6
non-severe -> severe	2	8.7
moderate -> severe	2	8.7
Total	23	100
Forward to moderate		
no-human-disease -> moderate	9	42.9
non-severe -> moderate	8	38.1
severe -> moderate	4	19.0
Total	21	100
Forward to non-severe		
no-human-disease -> non-severe	68	79.1
moderate -> non-severe	8	9.3
severe -> non-severe	10	11.6
Total	86	100
Forward from no-human-disease		
no-human-disease -> non-severe	68	70.8
no-human-disease -> moderate	9	9.4
no-human-disease -> severe	19	19.8
Total	96	100

Using the transition counts from **Table 1**, the association between having a non-human-infective ancestor node and a forward transition to any of the virulence classes was assessed (**Table 2**). Severe viruses or clades were more likely to evolve from a non-human-infective ancestor compared to moderate and non-severe viruses combined (odds ratio (OR) 1.84, 95% confidence interval (CI) 0.55 – 8.06, $p = 0.43$). Similarly, non-severe viruses or clades were also more likely to have evolved from a non-human-infective ancestor (OR 2.15, 95% CI, 0.89 – 5.19, $p = 0.09$). Yet, neither of these associations were statistically significant. Moderate viruses or clades, on the other hand, were significantly less likely to have a non-human-infective parent node compared to severe on non-severe viruses combined (OR 0.19, 95% CI, 0.06 – 0.57, $p = 0.010$).

Table 2: Relationship between human-infectivity of the ancestral parent node and subsequent virulence shift. Counts are derived from **Table 1**. “Forward to other virulence class” excludes the no-human-disease class.

a. Forward to severe

	Forward to severe	Forward to other virulence class	Total
Transition from no-human-disease	19	77	96
Transition from non-severe or moderate	4	30	34
Total	23	107	130

b. Forward to moderate

	Forward to moderate	Forward to other virulence class	Total
Transition from no-human-disease	9	87	96
Transition from non-severe or severe	12	22	34
Total	21	109	130

c. Forward to non-severe

	Forward to non-severe	Forward to other virulence class	Total
Transition from no-human-disease	68	28	96
Transition from moderate or severe	18	16	34
Total	86	44	130

Discussion

Key results

RNA viruses display large natural variation in disease severity upon human infection. Despite the importance of understanding RNA virus virulence in humans, comparative studies that examine how the existing variation in RNA virus human disease severity might have evolved are lacking. This study has characterized the frequency and distribution of virulence shifts across 40 viral genera containing human-infective RNA virus species. By fitting evolutionary discrete traits models on Bayesian phylogenetic trees, virulence shifts were investigated on a macroevolutionary scale. This study finds that large changes in virulence after a virus or viral lineage has evolved human-infectivity are infrequent and that 83% of viruses and lineages causing severe disease in humans are likely to have evolved from ancestral viruses unable to infect humans. Two virulence shifts in which non-severe human-infective viruses evolved to become more severe were observed and ten shifts in which severe viruses evolved to become less severe were observed, although 80 % of these were found in the *Flavivirus* genus. Moderate virulence shifts, i.e. an increase in virulence from non-severe to moderate, or a decrease in virulence from severe to moderate, were more balanced with 8 and 4 transitions respectively. When transitions from non-human-infective were stratified by envelope, genome and transmission mode, no transitions to severe were found for non-enveloped, dsRNA and vector-borne viruses.

Evolution of severe viruses

The finding that most severe viruses have directly evolved from non-human-infective viruses and not from other less severe human-infective viruses is broadly in line with the theory that novel associations between a host and parasite result in high levels of virulence (Read, 1994; Alizon et al., 2009). High profile case studies provide supporting evidence for this theory. For example, Nipah virus of the *Henipavirus* genus can be lethal in humans, whereas infection in its natural host manifest itself as a subclinical infection (Middleton et al., 2007). Similarly, although not included in this study, human immunodeficiency virus (HIV), when untreated, almost always progresses to AIDS in humans, whereas natural infection with the closely related simian immunodeficiency virus (SIV) persist in African non-human primates without causing severe disease (Silvestri et al., 2007). Evolutionary theory can help explain

this observed relationship between high virulence and spill-over into humans. Novel host-parasite interactions have not been subject to long term selection pressures and consequently a virus in a novel host has not been able to maximize its between-host transmission potential which could result in maladaptive viral virulence (Geoghegan and Holmes, 2018). It has to be noted though, that this observed relationship may be confounded by ascertainment bias as novel interactions resulting in high virulence are more likely to be reported. It is also unlikely that virulence evolution can be understood within a single, abstracted, theoretical framework, yet the general trend in this dataset is supportive of the notion that viruses causing severe disease in humans are likely to have evolved from an ancestral viral species that did not have the ability to infect humans, rather than from an ancestral viral species that did have the ability to infect humans but did not cause severe disease.

Infrequent virulence shift after evolving human-infectivity

This study also finds that virulence shifts from non-severe to severe and moderate to severe are infrequent, suggesting that once a virus has evolved human infectivity, it generally does not evolve to become more virulent. This seems to be in line with the theory that pathogen's virulence is restricted or, at least, that its virulence remains at an intermediate level influenced by the fitness costs and benefits associated with higher virulence (Read, 1994; Alizon et al., 2009). Although an abstraction and subject to assumptions, a virus's fitness, in epidemiological terms, can be expressed by its reproductive number R_0 (Cressler et al., 2015). R_0 , for simple Susceptible, Infectious or Recovered (SIR) disease dynamics, can be calculated using the equation: $R_0 = \frac{\beta S}{\mu + \nu + \gamma}$. Where β is the transmission rate, S is the density of susceptible individuals in the population, γ is the rate at which an infected host clears the disease, μ is the background mortality rate and ν is the mortality rate due to infection i.e., its virulence. Theory suggests that a virus's fitness, i.e. R_0 , should be maximized by natural selection (Schmid-Hempel, P., 2021). Evolving higher virulence can be beneficial for increasing R_0 as it increases the likelihood of transmission due to an increased time to immune clearance. At the same time, evolving higher virulence could also decrease transmission due to early host death. Therefore, natural selection results in a balance between the costs and benefits of evolving higher virulence resulting in constrained virulence evolution (Read, 1994; Alizon et al., 2009).

Virulence potential defined by viral genus

It was also found that the transition type from non-human-infective to any of the virulence classes is homogenous for 83% (33/40) of viral genera. This could indicate that the 'virulence potential', i.e., the allowed range of viral virulence for a virus species, is largely determined by its taxonomic group. A similar line of thought was explored by Washburne et al. (2018) who hypothesized that certain viral taxonomic groups have an inherently higher risk of being zoonotic. Using a phylofactorization algorithm, which iteratively identifies the most important clades on a phylogenetic tree driving variation in trait data through their associations with an outcome variable, Washburne et al. (2018) found that certain viral taxonomic groups indeed have a higher risk of being zoonotic; with *Togavirus*, *Flavivirus* and *Orthobunyavirus* having the highest risk (Washburne et al., 2018; Washburne et al., 2019). Interestingly, this study inferred a human-infective ancestral root state for two of the high-risk genera identified by Washburn et al. (2018), i.e. *Flavivirus* and *Togavirus*. Human-infectivity also evolved at a deep internal node for the third high risk clade; the *Orthobunyavirus* (**Figure 11a**). This observation seems to support the finding of Washburne et al. (2018) that these taxonomic groups have a spill-over potential into humans given that their ability to infect humans evolved early on.

Spill-over risk of a taxonomic group is likely determined by the presence of a conserved viral protein in member species which can bind human receptors facilitating human infection. Member species of the *Togavirus* genus, for example, are for the most part vector-borne viruses with a broad host range and express a receptor binding E2 glycoprotein protein capable of binding to a range of receptors found on most mammalian cell types (van Duijl-Richter et al., 2015; Klimstra et al., 2003). Similarly, the 'virulence potential' of a viral taxonomic group can relate to the presence of a viral protein that is able to interact with the human immune system which can cause subsequent pathology.

It is not unlikely that relatedness among viral species influences virulence. For example, using an experimental set-up in which 48 related species of *Drosophilidae* were infected with Drosophila C virus (DCV), it was found that DCV's virulence was most similar in closely related *Drosophilidae* species. From this, Longdon et al. (2015) postulated that if a virus causes high levels of virulence in any given host species, it

will typically cause similar levels of virulence in closely related host. This study has effectively looked at the inverse of this statement and suggest that related viral species are likely to evolve similar level of virulence in humans.

Limitations

It is important to acknowledge some major limitations of this study. Firstly, the definitions used to classify virus species into distinct virulence classes are inherently broad and therefore do not capture nuanced differences in disease severity between virus species. For example, epidemiological studies employing survival analysis report an increased risk of mortality when infected with the SARS-CoV-2 alpha variant compared to wildtype (Challen et al., 2021; Davies et al., 2021), indicative of increased virulence evolution (Alizon and Sofonea, 2021). Yet, such a shift would not be detected in this study given the broad discrete virulence categories used. This likely explains why limited transitions were found from human-infective viruses to any of the virulence classes.

Furthermore, the disease severity classifications are based on mortality in healthy adults and do not take into account long term morbidity from viral infection and mortality in vulnerable groups. This means that viruses classified as non-severe can still cause significant morbidity. For example, *Zika virus* is classified as non-severe in this study despite its association with microcephaly in neonates (Mlakar et al., 2016). Another limitation is related to data quality. Virulence classifications were partly done based on Case Fatality Ratios (CFR), which is the proportion of those diagnosed with an infection and who subsequently die. CFR can be unreliable for rare infections, which are also included in this study, for example, there is only one documented human case of *Tai Forest ebolavirus* infection in humans (Formenty et al., 1999). The classification system also assumes disease severity is product of a single virus species and does not consider co-infection. Despite these limitations, these data reflect our current understanding of disease severity upon human-infection based on primary epidemiological literature.

Results also need to be interpreted in a specific time frame. Data on viral species reflect the current knowledge of September 2021, yet there are continuous changes in viral taxonomy and discovery, making it difficult to compare results if a similar

analysis was redone in the future (Gorbalenya et al., 2020; Walker et al., 2022). This study also likely suffers from the sampling bias described in Wille et al., (2021). Wille et al. (2021) argue that our knowledge of viral diversity is outpacing the rate at which the ICTV is able to classify viral species resulting in an under-sampling bias in ICTV data. This limitation is somewhat mitigated in this study, given that for non-human-infective RNA virus species all available NCBI GenBank sequences were queried, yet human-infective viruses in the dataset are all ICTV-recognised species.

Another methodological consideration is the assumption that the most probable virulence trait label at each ancestral node in the phylogenetic is indeed the true virulence trait label. This assumption is reasonable when a particular trait state has a high probability, however it becomes more problematic if two trait states have similar probabilities. For example, the ancestral root state of the *Rotavirus* genus phylogenetic tree had a 53% posterior probability of being “no-human-disease” and 47% posterior probability of being “non-severe” (**Supplementary Table 2**). This analysis, based on the assumption that the most probable state is indeed the true state, would infer the root state to be “no-human-disease”, yet it does not convey the uncertainty surrounding that inference. Future work could include a sensitivity analysis in which only high probability nodes are examined in counting transition state counts and compare them to the results presented here.

Conclusion

This study has characterized the frequency and distribution of virulence shifts across 40 viral genera containing human-infective RNA viruses and adds an evolutionary approach to a broader framework of comparative studies aimed at understanding RNA virus virulence in humans. Findings suggest that, from a macroevolutionary viewpoint, the evolution of large virulence shifts after a virus or viral lineage has evolved human-infectivity are infrequent. Severe viruses were overrepresented in certain viral genera and were more likely to evolve from non-human-infective ancestors. More generally, this study highlights the diversity of virulence of human-infective RNA viruses and has identified trends on the origins of RNA viruses that cause disease in humans.

References

- Alizon, S. and Sofonea, M. T. (2021). SARS-CoV-2 virulence evolution: Avirulence Theory, immunity and trade-offs. *Journal of Evolutionary Biology*, 34(12), 1867–1877.
- Alizon, S., Hurford, A., Mideo, N. and Van Baalen, M. (2009). Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *Journal of Evolutionary Biology*, 22(2), 245-259.
- Brault, A. C., Huang, C. Y.-H., Langevin, S. A., Kinney, R. M., Bowen, R. A., Ramey, W. N., Panella, N. A., Holmes, E. C., Powers, A. M., and Miller, B. R. (2007). A single positively selected West Nile viral mutation confers increased virogenesis in American crows. *Nature Genetics*, 39(9), 1162–1166.
- Brierley, L., Pedersen, A. and Woolhouse, M. (2019). Tissue tropism and transmission ecology predict virulence of human RNA viruses. *PLoS Biology*, 17(11), p.e3000206.
- Brister, J. R., Ako-Adjei, D., Bao, Y. and Blinkova, O. (2015). NCBI viral genomes resource. *Nucleic Acids Research*, 43(Database issue), D571–D577.
- Carlson, C., Zipfel, C., Garnier, R. and Bansal. S. (2019). Global estimates of mammalian viral diversity accounting for host sharing. *Nature Ecology and Evolution*, 3(7), 1070-1075.
- Carroll, D., Daszak, P., Wolfe, N. D., Gao, G. F., Morel, C. M., Morzaria, S., Pablos Méndez, A., Tomori, O. and Mazet, J. A. (2018). The Global Virome Project. *Science*, 359(6378), 872–874.
- Challen, R., Brooks-Pollock, E., Read, J., Dyson, L., Tsaneva-Atanasova, K. and Danonm, L. (2021). Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. *BMJ*; 372, n579.

Cressler, C., Mcleod, D., Rozins, C., Van Den Hoogen, J. and Day, T. (2015). The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. *Parasitology*, 143(7), 915-930.

Davies, N. G., Jarvis, C. I., Edmunds, W. J., Jewell, N. P., Diaz-Ordaz, K. and Keogh, R. H. (2021). Increased mortality in community-tested cases of SARS-COV-2 lineage B.1.1.7. *Nature*, 593(7858), 270–274.

Day, T. (2002). The Evolution of Virulence in Vector-Borne and Directly Transmitted Parasites. *Theoretical Population Biology*, 62(2), 199-213.

Dong, Z., Yang, M., Wang, Z., Zhao, S., Xie, S., Yang, Y., Liu, G., Zhao, S., Xie, J., Liu, Q. and Wang, Y. (2021). Human Tacheng Tick Virus 2 Infection, China, 2019. *Emerging Infectious Diseases*, 27(2), 594–598.

Felsenstein, J. (2004) *Inferring Phylogenies*. Sinauer Associates Inc., Massachusetts; 664 pp.

Formenty, P., Hatz, C., Le Guenn, B., Stoll. A., Rogenmoser, P. and Widmer, A. (1999). Human Infection Due to Ebola Virus. Subtype Côte d'Ivoire: Clinical and Biologic Presentation. *The Journal of Infectious Diseases*, 179(s1), S48-S53.

Geoghegan, J. L., Senior, A. M., Di Giallonardo, F. and Holmes, E. C. (2016). Virological factors that increase the transmissibility of emerging human viruses. *Proceedings of the National Academy of Sciences*, 113(15), 4170–4175.

Geoghegan, J. and Holmes, E. (2018). The phylogenomics of evolving virus virulence. *Nature Reviews Genetics*, 19(12), 756-769.

Gorbalenya, A. E., Krupovic, M., Mushegian, A., Kropinski, A. M., Siddell, S. G., Varsani, A., Adams, M. J., Davison, A. J., Dutilh, B. E., Harrach, B., Harrison, R. L., Junglen, S., King, A. M., Knowles, N. J., Lefkowitz, E. J., Nibert, M. L., Rubino, L., Sabanadzovic, S., Sanfaçon, H., ... Kuhn, J. H. (2020). The new scope of virus taxonomy: Partitioning the virosphere into 15 hierarchical ranks. *Nature Microbiology*, 5(5), 668–674.

Grard, G., Moureau, G., Charrel, R. N., Holmes, E. C., Gould, E. A. and de Lamballerie, X. (2010). Genomics and evolution of Aedes-borne flaviviruses. *The Journal of General Virology*, 91(Pt 1), 87–94.

Groseth, A., Mampilli, V., Weisend, C., Dahlstrom, E., Porcella, S. F., Russell, B. J., Tesh, R. B. and Ebihara, H. (2014). Molecular characterization of human pathogenic bunyaviruses of the Nyando and Bwamba/Pongola virus groups leads to the genetic identification of Mojuí dos Campos and Kaeng Khoi virus. *PLoS Neglected Tropical Diseases*, 8(9), e3147.

Guth, S., Visher, E., Boots, M. and Brook. C. (2019). Host phylogenetic distance drives trends in virus virulence and transmissibility across the animal–human interface. *Philosophical Transactions of The Royal Society B: Biological Sciences*, 374(1782), 20190296.

Harvey, P. and Pagel, M. (1991). *The comparative method in evolutionary biology*. Oxford: Oxford University Press.

Harmon, L.J. (2019) *Phylogenetic comparative methods*. Minneapolis. MN: Open Textbook Library.

Hayes, E. B., Komar, N., Nasci, R. S., Montgomery, S. P., O'Leary, D. R. and Campbell, G. L. (2005). Epidemiology and transmission dynamics of West Nile virus disease. *Emerging Infectious Diseases*, 11(8), 1167–1173.

Katoh, K. and Standley, D. M. (2013). MAFFT multiple sequence alignment software version 7: improvements in performance and usability. *Molecular Biology and Evolution*, 30(4), 772–780.

Klimstra, W. B., Nangle, E. M., Smith, M. S., Yurochko, A. D. and Ryman, K. D. (2003). DC-SIGN and L-SIGN can act as attachment receptors for alphaviruses and distinguish between mosquito cell- and mammalian cell-derived viruses. *Journal of Virology*, 77(22), 12022–12032.

Lloyd-Smith, J. O., George, D., Pepin, K. M., Pitzer, V. E., Pulliam, J. R., Dobson, A. P., Hudson, P. J. and Grenfell, B. T. (2009). Epidemic dynamics at the human-animal interface. *Science*, 326(5958), 1362–1367.

Longdon, B., Hadfield, J. D., Day, J. P., Smith, S. C., McGonigle, J. E., Cogni, R., Cao, C. and Jiggins, F. M. (2015). The causes and consequences of changes in virulence following pathogen host shifts. *PLoS Pathogens*, 11(3), e1004728.

Lu, L., Brierley, L., Robertson, G., Zhang, F., Lycett, S., Smith, D., Chase-Topping, M., Simmonds, P. and Woolhouse, M. (2019). Evolutionary origins of epidemic potential among human RNA viruses. *bioRxiv* 771394.

Lewis, P.O. 2001. A likelihood approach to estimating phylogeny from discrete morphological characteristics data, *Systematic Biology*, 50:913-925.

Miranda, M. E., Ksiazek, T. G., Retuya, T. J., Khan, A. S., Sanchez, A., Fulhorst, C. F., Rollin, P. E., Calaor, A. B., Manalo, D. L., Roces, M. C., Dayrit, M. M. and Peters, C. J. (1999). Epidemiology of Ebola (subtype reston) virus in the Philippines, 1996. *The Journal of Infectious Diseases*, 179(s1).

Middleton, D. J., Morrissy, C. J., van der Heide, B. M., Russell, G. M., Braun, M. A., Westbury, H. A., Halpin, K. and Daniels, P. W. (2007). Experimental nipah virus infection in pteropid bats (pteropus poliocephalus). *Journal of Comparative Pathology*, 136(4), 266–272.

Minin, V. N. and Suchard, M. A. (2008). Fast, accurate and simulation-free stochastic mapping. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 363(1512), 3985–3995.

Mlakar, J., Korva, M., Tul, N., Popović, M., Poljšak-Prijatelj, M., Mraz, J., Kolenc, M., Resman Rus, K., Vesnaver Vipotnik, T., Fabjan Vodušek, V., Vizjak, A., Pižem, J., Petrovec, M. and Avšič Županc, T. (2016). Zika virus associated with microcephaly. *New England Journal of Medicine*, 374(10), 951–958.

Pagel, M. (1994). Detecting correlated evolution on phylogenies: A general method for the comparative analysis of discrete characteristics. *Proceedings of The Royal Society of London. Series B: Biological Sciences*, 255:37-45.

Read A. F. (1994). The evolution of virulence. *Trends in Microbiology*, 2(3), 73–76.

Schmid-Hempel, P (2021). 'Virulence evolution', *Evolutionary Parasitology: The Integrated Study of Infections, Immunology, Ecology, and Genetics*, 2nd edn (Oxford, 2021).

Silvestri, G., Paiardini, M., Pandrea, I., Lederman, M. M., and Sodora, D. L. (2007). Understanding the benign nature of SIV infection in natural hosts. *Journal of Clinical Investigation*, 117(11), 3148–3154.

Smithburn, K.C., Hughes, T.P., Burke, A. W. and Paul, J.H. (1940). A Neurotropic Virus Isolated from the Blood of a Native of Uganda, *The American Journal of Tropical Medicine*, s1-20(4), 471-492.

Suchard M.A., Lemey P., Baele G., Ayres D.L., Drummond A.J. and Rambaut A. (2018). Bayesian phylogenetic and phylodynamic data integration using BEAST 1.10, *Virus Evolution* 4, vey016.

van Duijl-Richter, M. K., Hoornweg, T. E., Rodenhuis-Zybert, I. A., and Smit, J. M. (2015). Early Events in Chikungunya Virus Infection-From Virus Cell Binding to Membrane Fusion. *Viruses*, 7(7), 3647–3674.

Van Kerkhove, M. D., Bento, A. I., Mills, H. L., Ferguson, N. M., and Donnelly, C. A. (2015). A review of epidemiological parameters from ebola outbreaks to inform early public health decision-making. *Scientific Data*, 2(1).

Walker, P. J., Siddell, S. G., Lefkowitz, E. J., Mushegian, A. R., Adriaenssens, E. M., Alfenas-Zerbini, P., Dempsey, D. M., Dutilh, B. E., García, M. L., Curtis Hendrickson, R., Junglen, S., Krupovic, M., Kuhn, J. H., Lambert, A. J., Łobocka, M., Oksanen, H. M., Orton, R. J., Robertson, D. L., Rubino, L., ... Zerbini, F. M. (2022). Recent

changes to virus taxonomy ratified by the International Committee on Taxonomy of Viruses (2022). *Archives of Virology*, 167(11), 2429–2440.

Walker, P. J., Siddell, S. G., Lefkowitz, E. J., Mushegian, A. R., Adriaenssens, E. M., Alfenas-Zerbini, P., Davison, A. J., Dempsey, D. M., Dutilh, B. E., García, M. L., Harrach, B., Harrison, R. L., Hendrickson, R. C., Junglen, S., Knowles, N. J., Krupovic, M., Kuhn, J. H., Lambert, A. J., Łobocka, M., Nibert, M. L., ... Zerbini, F. M. (2021). Changes to virus taxonomy and to the International Code of Virus Classification and Nomenclature ratified by the International Committee on Taxonomy of Viruses (2021). *Archives of virology*, 166(9), 2633–2648.

Washburne, A. D., Crowley, D. E., Becker, D. J., Olival, K. J., Taylor, M., Munster, V. J. and Plowright, R. K. (2018). Taxonomic patterns in the zoonotic potential of mammalian viruses. *PeerJ*, 6.

Washburne, A. D., Silverman, J. D., Morton, J. T., Becker, D. J., Crowley, D., Mukherjee, S., David, L. A. and Plowright, R. K. (2019). Phylofactorization: A graph partitioning algorithm to identify phylogenetic scales of ecological data. *Ecological Monographs*, 89(2).

Wille, M., Geoghegan, J.L. and Holmes, E.C. (2021) “How accurately can we assess zoonotic risk?,” *PLOS Biology*, 19(4).

Williams, M. C., Woodall, J. P. and Corbet, P. S. (1965). Nyando virus: a hitherto undescribed virus isolated from *Anopheles funestus* giles collected in kenya. *Archiv fur die gesamte Virusforschung*, 15, 422–427.

Woolhouse, M. E., Adair, K. and Brierley, L. (2013). RNA Viruses: A Case Study of the Biology of Emerging Infectious Diseases. *Microbiology spectrum*, 1(1), 10.1128/microbiolspec,OH-0001-2012.

Woolhouse, M. E., Brierley, L., McCaffery, C. and Lycett, S. (2016). Assessing the Epidemic Potential of RNA and DNA Viruses. *Emerging Infectious Diseases*, 22(12), 2037–2044.

Woolhouse, M. E. J., and Brierley, L. (2018). Epidemiological characteristics of human-infective RNA viruses. *Scientific Data*, 5, 180017.

Zhang, F., Chase-Topping, M., Guo, C., van Bunnik, B., Brierley, L. and Woolhouse, M. (2020). Global discovery of human-infective RNA viruses: A modelling analysis. *PLOS Pathogens*, 16(11), e1009079.

Supplementary Materials

Supplementary Table 1: Virus species (n=579) and virulence category classification used in data analyses. Virus species include both species recognized by the ICTV and species that are not (yet) recognized by the ICTV.

Family	Genus	Species	Virulence category
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Human coronavirus 229E</i>	non-severe
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Human coronavirus NL63</i>	non-severe
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Alphacoronavirus 1</i>	non-severe
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Bat coronavirus CDPHE15</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Bat coronavirus HKU10</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Rhinolophus ferrumequinum alphacoronavirus HuB-2013</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Lucheng Rn rat coronavirus</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Mink coronavirus 1</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Miniopterus bat coronavirus 1</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Myotis ricketti alphacoronavirus Sax-2011</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Nyctalus velutinus alphacoronavirus SC-2013</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Pipistrellus kuhlii coronavirus 3398</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>NL63-related bat coronavirus strain BtKYNL63-9b</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Sorex araneus coronavirus T14</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Suncus murinus coronavirus X74</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Miniopterus bat coronavirus HKU8</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Porcine epidemic diarrhea virus</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Scotophilus bat coronavirus 512</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Rhinolophus bat coronavirus HKU2</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Bat coronavirus 1A</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Bat coronavirus 1B</i>	no-human-disease
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	<i>Human coronavirus 229E like</i>	no-human-disease
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Barmah Forest virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Chikungunya virus</i>	moderate

<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Eastern equine encephalitis virus</i>	severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Everglades virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Getah virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Highlands J virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Madariaga virus</i>	moderate
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Mayaro virus</i>	moderate
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Middelburg virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Mosso das Pedras virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Mucambo virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Ndumu virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Onyong-nyong virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Pixuna virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Rio Negro virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Ross River virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Semliki Forest virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Sindbis virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Tonate virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Una virus</i>	non-severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Venezuelan equine encephalitis virus</i>	moderate
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Western equine encephalitis virus</i>	severe
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Whataroa virus</i>	non-severe
<i>Picornaviridae</i>	<i>Aphthovirus</i>	<i>Bovine rhinitis A virus</i>	no-human-disease
<i>Picornaviridae</i>	<i>Aphthovirus</i>	<i>Bovine rhinitis B virus</i>	no-human-disease
<i>Picornaviridae</i>	<i>Aphthovirus</i>	<i>Equine rhinitis A virus</i>	non-severe
<i>Picornaviridae</i>	<i>Aphthovirus</i>	<i>Foot-and-mouth disease virus</i>	non-severe
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Betacoronavirus 1</i>	non-severe
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>China Rattus coronavirus HKU24</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Human coronavirus HKU1</i>	non-severe
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Murine coronavirus</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Myodes coronavirus 2JL14</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Bat Hp-betacoronavirus Zhejiang2013</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Hedgehog coronavirus 1</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Middle East respiratory syndrome-related coronavirus</i>	severe
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Pipistrellus bat coronavirus HKU5</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Tylonycteris bat coronavirus HKU4</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Eidolon bat coronavirus C704</i>	no-human-disease

<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Rousettus bat coronavirus GCCDC1</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Rousettus bat coronavirus HKU9</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Severe acute respiratory syndrome-related coronavirus</i>	severe
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Human coronavirus 229E like</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Ghana348</i>	no-human-disease
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	<i>Eidolon bat coronavirus/Kenya/KY24/2006</i>	no-human-disease
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus E</i>	no-human-disease
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus F</i>	no-human-disease
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus A</i>	non-severe
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus B</i>	moderate
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus C</i>	no-human-disease
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus D</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus A</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus B</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus D</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus E</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus F</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus zj 1</i>	non-severe
<i>Picornaviridae</i>	<i>Cosavirus</i>	<i>Cosavirus JMY 2014</i>	non-severe
<i>Filoviridae</i>	<i>Ebolavirus</i>	<i>Bombali ebolavirus</i>	no-human-disease
<i>Filoviridae</i>	<i>Ebolavirus</i>	<i>Bundibugyo ebolavirus</i>	severe
<i>Filoviridae</i>	<i>Ebolavirus</i>	<i>Reston ebolavirus</i>	non-severe
<i>Filoviridae</i>	<i>Ebolavirus</i>	<i>Sudan ebolavirus</i>	severe
<i>Filoviridae</i>	<i>Ebolavirus</i>	<i>Tai Forest ebolavirus</i>	severe
<i>Filoviridae</i>	<i>Ebolavirus</i>	<i>Zaire ebolavirus</i>	severe
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus A</i>	moderate
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus B</i>	moderate
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus C</i>	moderate
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus D</i>	non-severe
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus E</i>	non-severe
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus F</i>	no-human-disease
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus G</i>	no-human-disease
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus H</i>	no-human-disease
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus I</i>	no-human-disease
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus J</i>	no-human-disease

<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus K</i>	no-human-disease
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus L</i>	no-human-disease
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Rhinovirus A</i>	non-severe
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Rhinovirus B</i>	non-severe
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Rhinovirus C</i>	non-severe
<i>Picornaviridae</i>	<i>Enterovirus</i>	<i>Enterovirus sp.</i>	no-human-disease
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Entebbe bat virus</i>	no-human-disease
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Jutiapa virus</i>	no-human-disease
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Phnom Penh bat virus</i>	no-human-disease
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Spanish goat encephalitis virus</i>	no-human-disease
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Yokose virus</i>	no-human-disease
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Aroa virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Bagaza virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Cacipacore virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Israel turkey meningoencephalomyelitis virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Japanese encephalitis virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Kyasanur forest disease virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Louping ill virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Murray Valley encephalitis virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Omsk hemorrhagic fever virus</i>	moderate
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Powassan virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>St. Louis encephalitis virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Tembusu virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Tick borne encephalitis virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Usutu virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Wesselsbron virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>West Nile virus</i>	moderate
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Dengue virus</i>	moderate
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Yellow fever virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Zika virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Banji virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Edge Hill virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Kokobera virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Ntaya virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Rio Bravo virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Uganda S virus</i>	non-severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Gadgets Gully virus</i>	non-severe

<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Ilheus virus</i>	severe
<i>Flaviviridae</i>	<i>Flavivirus</i>	<i>Langat virus</i>	non-severe
<i>Henipavirus</i>	<i>Henipavirus</i>	<i>Cedar henipavirus</i>	no-human-disease
<i>Henipavirus</i>	<i>Henipavirus</i>	<i>Ghanaian bat henipavirus</i>	no-human-disease
<i>Henipavirus</i>	<i>Henipavirus</i>	<i>Hendra henipavirus</i>	severe
<i>Henipavirus</i>	<i>Henipavirus</i>	<i>Mojiang henipavirus</i>	no-human-disease
<i>Henipavirus</i>	<i>Henipavirus</i>	<i>Nipah henipavirus</i>	severe
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus A</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus B</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus C</i>	severe
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus D</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus E</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus F</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus G</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus H</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus I</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus J</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus K</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus L</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus M</i>	no-human-disease
<i>Flaviviridae</i>	<i>Hepacivirus</i>	<i>Hepacivirus N</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus A</i>	moderate
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus B</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus C</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus D</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus E</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus F</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus G</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus H</i>	no-human-disease
<i>Picornaviridae</i>	<i>Hepatovirus</i>	<i>Hepatovirus I</i>	no-human-disease
<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus A - human</i>	non-severe

<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus B</i>	no-human-disease
<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus C</i>	no-human-disease
<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus D</i>	no-human-disease
<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus E</i>	no-human-disease
<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus F</i>	no-human-disease
<i>Picornaviridae</i>	<i>Kobuvirus</i>	<i>Aichivirus A non-human</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Gannoruwa bat lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Lleida bat lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Aravan lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Australian bat lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Bokeloh bat lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Duvenhage lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>European bat 1 lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>European bat 2 lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Ikoma lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Irkut lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Khujand lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Lagos bat lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Mokola lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Rabies lyssavirus</i>	severe
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Shimoni bat lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>Taiwan bat lyssavirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	<i>West Caucasian bat lyssavirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 1</i>	non-severe
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 2</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 3</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 4</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 5</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 6</i>	non-severe
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 7</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 8</i>	non-severe
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 9</i>	non-severe

<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 10</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 11</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 12</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 13</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 14</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 15</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 16</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 17</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 18</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 19</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Bovine astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Feline astrovirus D1</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Fox astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mouse astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Murine astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Porcine astrovirus 2</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Porcine astrovirus 3</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Porcine astrovirus 4</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Porcine astrovirus 5</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Porcupine astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Rat astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Yak astrovirus</i>	no-human-disease
<i>Astroviridae</i>	<i>Mamastrovirus</i>	<i>Mamastrovirus 20</i>	non-severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Alxa mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Chevrier mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Gairo mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Loei River mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Planalto mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Ryukyu mammarenavirus</i>	no-human-disease

<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Solwezi mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Souris mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Tacaribe mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Allpahuayo mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Argentinian mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Bear Canyon mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Brazilian mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Cali mammarenavirus</i>	non-severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Chapare mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Cupixi mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Guanarito mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Lassa mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Latino mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Lujo mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Luna mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Lunk mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Lymphocytic choriomeningitis mammarenavirus</i>	moderate
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Machupo mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Mariental mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Merino Walk mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Mobala mammarenavirus</i>	non-severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Mopeia mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Okahandja mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Oliveros mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Paraguayan mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Piritai mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Serra do Navio mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Tamiami mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Wenzhou mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Whitewater Arroyo mammarenavirus</i>	severe
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Xapuri mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Dandenong virus</i>	no-human-disease

<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Morogoro virus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Praomys arenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Rat arenavirus 1</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Allpahuayo mammarenavirus</i>	no-human-disease
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	<i>Parana-mammarenavirus</i>	no-human-disease
<i>Pneumoviridae</i>	<i>Metapneumovirus</i>	<i>Avian metapneumovirus</i>	non-severe
<i>Pneumoviridae</i>	<i>Metapneumovirus</i>	<i>Human metapneumovirus</i>	non-severe
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Canine morbillivirus</i>	non-severe
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Cetacean morbillivirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Feline morbillivirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Measles morbillivirus</i>	moderate
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Phocine morbillivirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Rinderpest morbillivirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	<i>Small ruminant morbillivirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Norovirus</i>	<i>Norovirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Norovirus</i>	<i>Norovirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Norovirus</i>	<i>Norovirus</i>	non-severe
<i>Caliciviridae</i>	<i>Norovirus</i>	<i>Norovirus</i>	non-severe
<i>Caliciviridae</i>	<i>Norovirus</i>	<i>Bat Norovirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Norovirus</i>	<i>Bovine calicivirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Great Island virus</i>	non-severe
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Yunnan orbivirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>African horse sickness virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Bluetongue virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Changuinola virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Corripata virus</i>	non-severe
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Epizootic hemorrhagic disease virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Equine encephalosis virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Lebombo virus</i>	non-severe
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Orungo virus</i>	non-severe
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Palyam virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Peruvian horse sickness virus</i>	no-human-disease

<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Umatilla virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orbivirus</i>	<i>Baku virus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 16</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 17</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 18</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 19</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 21</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 1</i>	non-severe
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 9</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 12</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	<i>Avian orthoavulavirus 13</i>	no-human-disease
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Mammalian 1 orthobornavirus</i>	non-severe
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Mammalian 2 orthobornavirus</i>	severe
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Passeriform 1 orthobornavirus</i>	no-human-disease
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Passeriform 2 orthobornavirus</i>	no-human-disease
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Psittaciform 1 orthobornavirus</i>	no-human-disease
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Psittaciform 2 orthobornavirus</i>	no-human-disease
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	<i>Waterbird 1 orthobornavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Acara orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Batama orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Benevides orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Bertioga orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Bushbush orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Capim orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Gamboa orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Jatobal orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Minatitlan orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Patois orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Peaton orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Tataguine orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Timboteua orthobunyavirus</i>	no-human-disease

<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Turlock orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Zegla orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Akabane orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Bunyamwera orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Bwamba orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Cache Valley orthobunyavirus</i>	moderate
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>California encephalitis orthobunyavirus</i>	severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Caraparu orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Catu orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Fort Sherman orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Guajara orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Guama orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Guaroa orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Ilesha orthobunyavirus</i>	moderate
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Jamestown Canyon orthobunyavirus</i>	moderate
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Kaeng Khoi orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Kairi orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Keystone orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>La Crosse orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Madrid orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Maguari orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Manzanilla orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Marituba orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Melao orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Mermet orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Minatitlan orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Nyando orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Oriboca orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Oropouche orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Schmallenberg orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Shuni orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Snowshoe hare orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Tacaiuma orthobunyavirus</i>	non-severe
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Tete orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Utinga orthobunyavirus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Wyeomyia orthobunyavirus</i>	non-severe

<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Mojui dos Campos virus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Pacui virus</i>	no-human-disease
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Tapirape virus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Asama orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Bruges orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Cao Bang orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Fugong orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Luxi orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Maporal orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Prospect Hill orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Tigray orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Andes orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Bayou orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Black Creek Canal orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Bowe orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Cano Delgadito orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Choclo orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Dobrava-Belgrade orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Hantaan orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Jeju orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Kenkeme orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Khabarovsk orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Laguna Negra orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Montano orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Puumala orthohantavirus</i>	moderate
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Rockport orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Sangassou orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Seoul orthohantavirus</i>	moderate
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Sin Nombre orthohantavirus</i>	severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Thailand orthohantavirus</i>	non-severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Tula orthohantavirus</i>	non-severe
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Altai orthohantavirus</i>	no-human-disease

<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Amur orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Camp Ripley orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Carrizal orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>CASV 2 orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Catacamas orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Eothenomys miletus hantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Hokkaido orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Huitzilac orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Kilimanjaro orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Muju orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Uluguru orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Ussuri orthohantavirus</i>	no-human-disease
<i>Hantaviridae</i>	<i>Orthohantavirus</i>	<i>Xinyi orthohantavirus</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	moderate
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	moderate
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	moderate
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	moderate
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	moderate
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus A</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus B</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus C</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>Orthohepevirus D</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>AlgSwe2012</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>kestrel/MR22</i>	no-human-disease
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	<i>little-egret/kocsag02</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Qalyub orthonairovirus</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Songling virus</i>	non-severe
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Dera Ghazi Khan orthonairovirus</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Hughes orthonairovirus</i>	no-human-disease

<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Kasokero orthonairovirus</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Keterrah orthonairovirus</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Sakhalin orthonairovirus</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Dugbe orthonairovirus</i>	non-severe
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Nairobi sheep disease orthonairovirus</i>	non-severe
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Thiafora orthonairovirus</i>	non-severe
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Crimean Congo hemorrhagic fever orthonairovirus</i>	severe
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Hazara orthonairovirus</i>	no-human-disease
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	<i>Issyk-kul orthonairovirus</i>	non-severe
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Bovine orthopneumovirus</i>	no-human-disease
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Human orthopneumovirus</i>	non-severe
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Murine orthopneumovirus</i>	no-human-disease
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Canine pneumovirus</i>	no-human-disease
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Bovine orthopneumovirus</i>	no-human-disease
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Human orthopneumovirus</i>	non-severe
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Murine orthopneumovirus</i>	no-human-disease
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	<i>Canine pneumovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Avian orthoreovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Baboon orthoreovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Broome orthoreovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Mammalian orthoreovirus</i>	non-severe
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Nelson Bay orthoreovirus</i>	non-severe
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Broome virus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Cangyuan orthoreovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Duck reovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Goose orthoreovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Muscovy duck reovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Pteropine orthoreovirus</i>	no-human-disease
<i>Reoviridae</i>	<i>Orthoreovirus</i>	<i>Pulau reovirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Human orthorubulavirus 2</i>	non-severe
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Human orthorubulavirus 4</i>	non-severe
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Mammalian orthorubulavirus 5</i>	non-severe

<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Mammalian orthorubulavirus 6</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Mapuera orthorubulavirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Mumps orthorubulavirus</i>	moderate
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Porcine orthorubulavirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	<i>Simian orthorubulavirus</i>	non-severe
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Achimota pararubulavirus 1</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Achimota pararubulavirus 2</i>	non-severe
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Hervey pararubulavirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Menangle pararubulavirus</i>	non-severe
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Sosuga pararubulavirus</i>	severe
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Teviot pararubulavirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Tioman pararubulavirus</i>	non-severe
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Tuhoko pararubulavirus 1</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Tuhoko pararubulavirus 2</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>Tuhoko pararubulavirus 3</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	<i>BtHa ParaV GD2012</i>	no-human-disease
<i>Picornaviridae</i>	<i>Parechovirus</i>	<i>Parechovirus A</i>	non-severe
<i>Picornaviridae</i>	<i>Parechovirus</i>	<i>Parechovirus B</i>	non-severe
<i>Picornaviridae</i>	<i>Parechovirus</i>	<i>Parechovirus C</i>	no-human-disease
<i>Picornaviridae</i>	<i>Parechovirus</i>	<i>Parechovirus D</i>	no-human-disease
<i>Picornaviridae</i>	<i>Parechovirus</i>	<i>Parechovirus E</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus A</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus B</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus C</i>	non-severe
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus D</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus E</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus F</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus G</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus H</i>	non-severe
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus I</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus J</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pegivirus</i>	<i>Pegivirus K</i>	no-human-disease

<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus A</i>	non-severe
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus B</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus C</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus D</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus E</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus F</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus G</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus H</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus I</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus J</i>	no-human-disease
<i>Flaviviridae</i>	<i>Pestivirus</i>	<i>Pestivirus K</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Anhanga phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Echarate phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Gabek phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Gordil phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Itaporanga phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Maldonado phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Punta Toro phlebovirus</i>	non-severe
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Rio Grande phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Saint Floris phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Urucuri phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Alenquer phlebovirus</i>	non-severe
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Arumowot phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Bujaru phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Candiru phlebovirus</i>	non-severe
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Icoaraci phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Itaituba phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Naples phlebovirus</i>	non-severe
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Salanga phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Sicilian phlebovirus</i>	non-severe
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Toscana phlebovirus</i>	non-severe

<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Urucuri phlebovirus</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Rift Valley fever phlebovirus</i>	moderate
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Phlebovirus GGP 2011a</i>	no-human-disease
<i>Phenuviridae</i>	<i>Phlebovirus</i>	<i>Salanga virus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Beihai picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Equine picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Human picobirnavirus</i>	non-severe
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Human picobirnavirus</i>	non-severe
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Avian picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Bovine picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Dromedary picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Equine picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Feline picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Fox picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Genet picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Microtus picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Otarine picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Porcine picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Primate picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Seal picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Turkey picobirnavirus</i>	no-human-disease
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	<i>Rodent picobirnavirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Bovine respirovirus 3</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Caprine respirovirus 3</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Human respirovirus 1</i>	non-severe
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Human respirovirus 3</i>	non-severe
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Murine respirovirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Porcine respirovirus 1</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Squirrel respirovirus</i>	no-human-disease
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	<i>Swine respirovirus 3</i>	no-human-disease
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus A</i>	non-severe

<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus B</i>	non-severe
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus C</i>	non-severe
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus D</i>	no-human-disease
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus F</i>	no-human-disease
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus G</i>	no-human-disease
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus H</i>	non-severe
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus I</i>	no-human-disease
<i>Reoviridae</i>	<i>Rotavirus</i>	<i>Rotavirus J</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GXIV</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GXII</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GIII</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GVI</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GXIII</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GIX</i>	no-human-disease
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GI</i>	non-severe
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GII</i>	non-severe
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GV</i>	non-severe
<i>Caliciviridae</i>	<i>Sapovirus</i>	<i>Sapovirus GIV</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>American bat vesiculovirus</i>	no-human-disease
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Alagoas vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Chandipura vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Cocal vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Indiana vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Isfahan vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Jurona vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Maraba vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>New Jersey vesiculovirus</i>	non-severe
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Piry vesiculovirus</i>	non-severe
<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>Feline calicivirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>Vesicular exanthema of swine virus</i>	non-severe
<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>Canine calicivirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>Canine vesivirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>Mink calicivirus</i>	no-human-disease
<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>San Miguel sea lion virus 8</i>	no-human-disease

<i>Caliciviridae</i>	<i>Vesivirus</i>	<i>Vesivirus ferret</i>	no-human-disease
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Supplementary Table 2: Probabilistic outputs of most likely ancestral root state of genus level phylogenies from Bayesian trait analyses in BEAST.

Family	Genus	Most likely ancestral state	Poster or probab ty no-human-d sease	Poster or probab ty non-severe	Poster or probab ty moderate	Poster or probab ty severe
<i>Togaviridae</i>	<i>Alphavirus</i>	non-severe	-	0.9655	0.0341	0.0004
<i>Paramyxoviridae</i>	<i>Orthoavulavirus</i>	no-human-d sease	0.6764	0.3236	-	-
<i>Coronaviridae</i>	<i>Betacoronavirus</i>	no-human-d sease	0.9983	0.0012	-	0.0005
<i>Picornaviridae</i>	<i>Cardiovirus</i>	no-human-d sease	0.7166	0.0811	0.2023	-
<i>Ebolavirus</i>	<i>Ebolavirus</i>	severe	0.0724	0.0967	-	0.8309
<i>Flaviviridae</i>	<i>Flavivirus</i>	severe	0.0884	0.2809	0.0036	0.6271
<i>Picornaviridae</i>	<i>Kobuvirus</i>	no-human-d sease	0.9567	0.0433	-	-
<i>Picornaviridae</i>	<i>Aphthovirus</i>	non-severe	0.4009	0.5991	-	-
<i>Picornaviridae</i>	<i>Enterovirus</i>	no-human-d sease	0.6696	0.3003	0.0301	-
<i>Picornaviridae</i>	<i>Hepatovirus</i>	no-human-d sease	0.8503	-	0.1497	-
<i>Hepeviridae</i>	<i>Orthohepevirus</i>	no-human-d sease	0.6641	-	0.3369	-
<i>Flaviviridae</i>	<i>Pegivirus</i>	no-human-d sease	-	0.4462	-	-
<i>Picobirnaviridae</i>	<i>Picobirnavirus</i>	no-human-d sease	0.9197	0.0803	-	-
<i>Caliciviridae</i>	<i>Vesivirus</i>	no-human-d sease	0.764	0.236	-	-
<i>Caliciviridae</i>	<i>Sapovirus</i>	no-human-d sease	0.6294	0.3706	-	-
<i>Flaviviridae</i>	<i>Hepacivirus</i>	no-human-d sease	-	-	-	0.4411
<i>Bornaviridae</i>	<i>Orthobornavirus</i>	no-human-d sease	0.9388	0.0326	-	0.0285
<i>Paramyxoviridae</i>	<i>Morbillivirus</i>	no-human-d sease	0.9822	0.0138	0.004	-
<i>Pneumoviridae</i>	<i>Orthopneumovirus</i>	no-human-d sease	0.6337	0.3663	-	-
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	no-human-d sease	0.716	0.2301	0.0087	-

<i>Hantaviridae</i>	<i>Orthohantavirus</i>	no-human-d sease	0.9472	0.002	0.0014	0.0538
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	no-human-d sease	0.5969	0.0766	0.0765	0.25
<i>Coronaviridae</i>	<i>Alphacoronavirus</i>	no-human-d sease	0.9933	0.0067	-	-
<i>Picornaviridae</i>	<i>Cosavirus</i>	non-severe	0	1	0	0
<i>Paramyxoviridae</i>	<i>Henipavirus</i>	no-human-d sease	0.9361	-	-	0.0639
<i>Rhabdoviridae</i>	<i>Lyssavirus</i>	no-human-d sease	0.7461	-	-	0.2539
<i>Astroviridae</i>	<i>Mamastrovirus</i>	no-human-d sease	0.7289	0.2711	-	-
<i>Caliciviridae</i>	<i>Norovirus</i>	no-human-d sease	0.775	0.2225	-	-
<i>Reoviridae</i>	<i>Orbivirus</i>	no-human-d sease	0.897	0.103	-	-
<i>Nairoviridae</i>	<i>Orthonairovirus</i>	no-human-d sease	0.5029	0.3759	-	0.1212
<i>Reoviridae</i>	<i>Orthoreovirus</i>	no-human-d sease	0.9659	0.0341	-	-
<i>Paramyxoviridae</i>	<i>Orthorubulavirus</i>	non-severe	0.2805	0.5851	0.1344	-
<i>Paramyxoviridae</i>	<i>Pararubulavirus</i>	no-human-d sease	0.6332	0.3327	-	0.0341
<i>Phenuviridae</i>	<i>Phlebovirus</i>	no-human-d sease	0.9693	0.0236	0.0071	-
<i>Paramyxoviridae</i>	<i>Respirovirus</i>	no-human-d sease	0.8017	0.1983	-	-
<i>Reoviridae</i>	<i>Rotavirus</i>	no-human-d sease	0.5288	0.4712	-	-
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	non-severe	0.3403	0.6597	-	-
<i>Flaviviridae</i>	<i>Pestivirus</i>	no-human-d sease	-	0.3623	-	-
<i>Picornaviridae</i>	<i>Parechovirus</i>	no-human-d sease	-	0.4181	-	-
<i>Pneumoviridae</i>	<i>Metapneumovirus</i>	non-severe	0	1	0	0

Supplementary Table 3: Newly identified, ICTV-recognised human-infective RNA virus species (n=41) in June 2021. These virus species were not present in the latest update of our inhouse human-infective RNA virus database by Zhang et al. (2020).

Family	Genus	Species
<i>Caliciviridae</i>	<i>Recovirus</i>	<i>Recovirus A</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus cameroonense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus carense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus italiense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus japanense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus peruense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus senegalense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus taiwanense</i>
<i>Kolmioviridae</i>	<i>Deltavirus</i>	<i>Deltavirus togense</i>
<i>Nairoviridae</i>	<i>Orthonaivirus</i>	<i>Issyk-kul orthonaivirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Apeu orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Batai orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Cache Valley orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Fort Sherman orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Ilesha orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Jamestown Canyon orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Keystone orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>La Crosse orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Lumbo orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Maguari orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Melao orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Snowshoe hare orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Tahyna orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Tataguine orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Trivittatus orthobunyavirus</i>
<i>Peribunyaviridae</i>	<i>Orthobunyavirus</i>	<i>Turlock orthobunyavirus</i>
<i>Phenuiviridae</i>	<i>Bandavirus</i>	<i>Bhanja bandavirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Adana phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Alenquer phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Chagres phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Cocle phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Echarate phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Maldonado phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Ntepes phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Sicilian phlebovirus</i>
<i>Phenuiviridae</i>	<i>Phlebovirus</i>	<i>Toscana phlebovirus</i>
<i>Phenuiviridae</i>	<i>Tanzavirus</i>	<i>Human tanzavirus</i>

<i>Phenuiviridae</i>	<i>Uukuvirus</i>	<i>Tacheng uukuvirus</i>
<i>Picornaviridae</i>	<i>Cardiovirus</i>	<i>Cardiovirus D</i>
<i>Rhabdoviridae</i>	<i>Vesiculovirus</i>	<i>Jurona vesiculovirus</i>
<i>Togaviridae</i>	<i>Alphavirus</i>	<i>Middelburg virus</i>