Ancient Epidemics in Bats Play a Role in Human Case Fatality Rate and Death Burden

Alysa Olivas, Salomé Arrieta, Tucson Magnet High School

Elise Lauterbur

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Introduction

Zoonotic viruses remain a topic of major concern over the past few years in response to the global outbreak of SARS-CoV-2. Bats are often at the center of the conversation of zoonotic viruses due to their reputation as hosts. Zoonotic viruses or zoonoses are viruses that can transfer to humans from animals. When contextualizing bats as hosts for zoonotic viruses, it is important to understand their species diversity, evolutionary history, and virulence. Bats, order *Chiroptera,* are often thought to have more zoonoses when compared to other mammals; however, it is important to consider the species diversity of *Chiroptera*. There are 1400 different species of bats, and given these circumstances bats do harbor a greater number of zoonoses due to their diversity (Streiker & Gilbert, et al., 2020). Viruses are a primary cause of adaptation in mammals, which consequently is what leads to the evolution of these different species (Enard et al., 2016). It is possible to understand the evolutionary history of bats relating to viruses by examining their virus interacting proteins (VIPs). Adaptation in VIPs is evidence of past interactions with those viruses and the adaptation strength can be used to determine the evolutionary history of that mammal with a type of virus. Bats host a significant amount of virulent viruses which is important when assessing the potential risk of outbreak (Guth et al., 2022).

This project assessed the relationship between ancient epidemics in mammals and case fatality rate (CFR) and death burden in humans. By understanding the interactions between VIPs in all mammals and the effects of the corresponding viruses on humans it is possible to contextualize if bats are unique hosts of zoonotic viruses. Using data from a study published in 2022 by Sarah Guth and others, as well as measurements of adaptation in VIPs in bats and other mammals, we are able to expand on understanding the effects of bats as hosts of zoonotic viruses. This analysis provides another way to assess the risk of zoonotic viruses when it comes to the concerns of the health and well being of humans. This study can help to provide a better understanding of what effects zoonotic viruses found in mammals have on humans and why some viruses may cause epidemics.

Through this project we explore if there is a correlation between VIP strength in mammals and CFR and death burden in humans. Based on the research that has been conducted thus far, we hypothesize that if there is greater strength of adaptation in VIPs associated with a type of virus, there will be an increase in CFR and death burdens in humans caused by that type of virus because this suggests that the virus has had a stronger overall effect on mammals through evolutionary history.

Methods

To answer the question "if there is a correlation between VIP strength in mammals and CFR and death burden in humans", data from previous research was utilized (Enard et al., 2016). The data from the Enard study will help to find how ancient epidemics affected mammals thousands of years ago. The Guth et al., 2022 study provided data about human CFR, virulence, and death burden for different viruses. The findings of the Guth et al. (2022) paper indicate that bat borne viruses are highly virulent as compared to other zoonotic viruses. We hope to further contextualize this by relating it to past epidemics in host species with the VIP data.

We performed two phylogenetically-informed regressions with these data. using the R statistical package (R Core Team (2021). This is a software environment that is often used for statistical analysis. Using this software environment will help to find the overall correlation that is being questioned as well as help to teach new skills involving data analysis.

This analysis was used to discover the possible correlation between ancient epidemics in bats (VIP adaptation strength) and CFR and death burden in humans. Phylogenetically-informed regressions take into account the evolutionary relatedness of species included in the analysis to better understand the relationships between the variables. We used two different R packages to create our models, phylogmm (Li and Bolker, 2019) and phytools (v0.7-70; Revell, 2012). and ggplot (v3. 3.3; Wickham, 2016). Because the Guth et al. 2022 data included measurements for multiple virus species within viral families, but the VIP data is per viral family, we averaged the CFR and death burden data across viral species within each viral family.

We tested what variables and their interactions created the best fitted model to understand what interactions played a role in human CFR and death burden. These variables included the VIP adaptation strength, the host order of the mammal species hosting the virus, and the order of the mammal species the VIP adaptation strength was measured in. We used the DHARMa (Hartig 2018) package to check the fit of our models to the data, and compared the log likelihood scores to compare models with different predictor variables. Upon choosing the best model we were able to see how different mammals were contributing to the integrated data as well as visualize both the CFR and death burden results using ggplot (v3. 3.3; Wickham, 2016).

Results

The best fitted model for CFR included VIP strength, host order, VIP measurement order, and the interactions between VIP strength and host order and VIP strength and measurement order. Upon analysis we found that CFR in humans changes based on how adapted to viruses bats are when they are the host. As VIP strength in bats increased so did human CFR. This was in contrast to the other mammals which appeared to show an opposite or no trend.

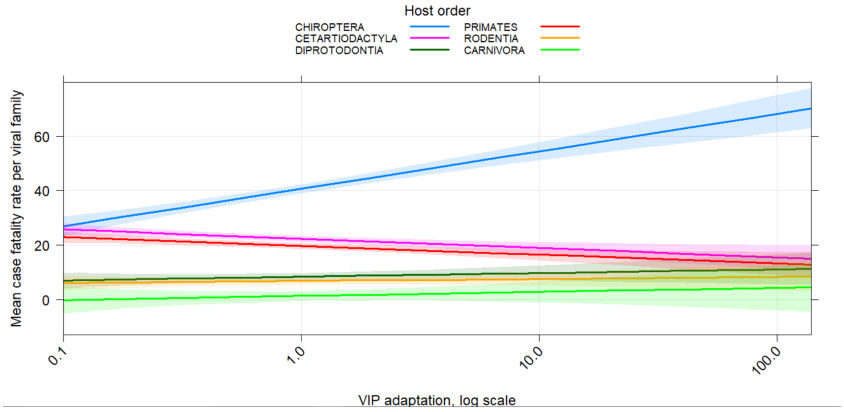

Fig. 1: This graph shows the relationship between the mean case fatality rate in humans (y-axis) and VIP adaptations (x-axis). The most noticeable line is the blue that represents chiroptera (bats) with the largest positive of the mammals represented in this graph.

The best fitted model produced for death burden included VIP strength, host order, and their interaction. In contrast to the relationship between VIP strength and CFR, we found that as VIP strength decreased in bats, the death burden increased in humans. We found in other

mammals there was some correlation between VIP strength and death burden but bats showed significant results in comparison.

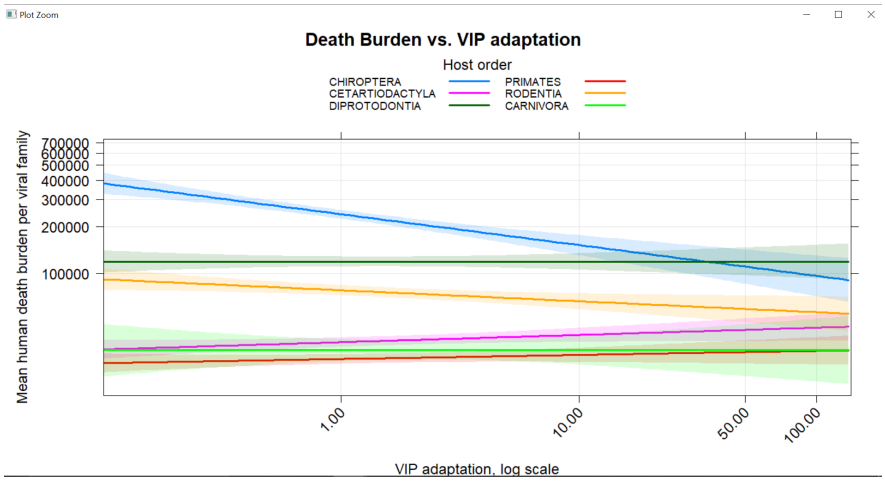

Fig. 2: From this graph it can be seen that chiroptera has a very clear negative slope, which shows that as there is greater VIP adaptation (x-axis), there is a decrease in human death burden (y-axis).

Discussion

Through the process of our research we found that our hypothesis was partially supported. The relationship between CFR and VIP strength fit our expectations that as VIP strength increased so did CFR. However our death burden results did not support our hypothesis, instead we found As VIP strength decreased death burden increased. It is possible to understand these results within the context of transmissibility of viruses. If a virus is highly transmissible it has a greater opportunity to kill more people even when the number of people killed per infection (CFR) is low. However, in order for a virus to continue infecting people it must adapt to not always kill its host. This balance could explain why zoonotic viruses in bats may have evolved to infect, but not necessarily kill more people. Unfortunately due to its complexity and a general lack of data we were unable to statistically test if VIP strength is also related to human transmissibility. This being said, our data suggests that transmissibility plays a vital role in zoonotic viruses hosted by bats.

The uniqueness of bats as hosts for zoonotic viruses was apparent in our research. When evaluating case fatality rate bats showed opposite trends compared to other mammals. Additionally, while in most mammals as VIP strength increased death burden decreased this

relationship was particularly significant in bats. This could suggest bats have a distinctive relationship with past epidemiological events.

Throughout the continuum of our research we encountered limitations in our data. By only being able to use the common variables between the Guth et al. 2022 and Enard data our own data set was limited. This prompted us to change our original methods to include all mammals and expand our database. Additionally as previously mentioned we had to exclude transmissibility from our question due to similar barriers. These limitations leave room for further exploration in the future.

Given the recent COVID-19 pandemic the study of zoonotic diseases remains pertinent. It is our hope that this study provides another way to understand spill over. As well as the possible risk of these viruses in bats

References

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