American Journal of Infectious Diseases and Microbiology, 2024, Vol. 12, No. 4, 99-103
Available online at http://pubs.sciepub.com/ajidm/12/4/3
Published by Science and Education Publishing
DOI:10.12691/ajidm-12-4-3

Did Previous Exposure to Bat Urine and Feces Influence the Disease Outcomes of COVID-19 Caused by the Novel SARS-CoV-2?

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Received October 04, 2024; Revised November 06, 2024; Accepted November 13, 2024

Abstract The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) had a significant impact on the lives of people throughout the world. Given the horrific nature of the initial phases of the pandemic wherein several people who were infected suffered from severe diseases that resulted in deaths, restriction of the movement of people in the form of lockdowns was imminent. COVID-19 was a global catastrophe resulting from a novel coronavirus potentially originating from bats. Despite significant advancements in understanding COVID-19 and SARS-CoV-2, several unanswered aspects like the evolution of a novel virus, potential animal reservoirs and carriers, immunological responses to infection, and causes for the variable clinical outcomes, among others remain to be completely understood. Another significant facet of the COVID-19 pandemic was the variable mortality rates among the infected populations and the reasons for the post-COVID effects on the recovered populations. Through this communication, we hypothesize and investigate the possibility of previous exposures to bat urine and feces influencing COVID-19 outcomes.

Keywords: *SRAS-CoV-2, COVID-19, pandemic, immunological responses, clinical outcomes, bat urine and feces, exposure, mortality rates*

Cite This Article: Venkataramana Kandi, “Did Previous Exposure to Bat Urine and Feces Influence the Disease Outcomes of COVID-19 Caused by the Novel SARS-CoV-2?.” *American Journal of Infectious Diseases and Microbiology*, vol. 12, no. 4 (2024): 99-103. doi: 10.12691/ajidm-12-4-3.

1. Introduction

Among the various aspects of the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the most intriguing thing was the complex nature of the COVID-19 disease pathogenesis and its clinical outcomes. The initial phases of the pandemic saw serious complications that led to the death of the infected persons. However, slowly and gradually, as the SARS-CoV-2 started spreading and infecting more and more people, physicians and scientists have noticed variable clinical outcomes among infected populations. This is evident by the occurrence of asymptomatic infections wherein infected persons showed no symptoms. Additionally, a few infected persons developed infections that resulted in mild symptoms that required no hospitalization. Strangely, some patients developed moderate to severe infections that required hospitalization and intensive care unit (ICU) admission and critical care treatment including intubation and mechanical respiratory support.

Most infections were averted courtesy of strict restrictions on people's movements in the form of lockdowns. Despite this, SARS-CoV-2 spread throughout the world and resulted in billions of infections and millions of deaths. Most infections associated with complications were noticed among aged populations and people with comorbidities. However, some infections among middle-aged persons and young individuals also resulted in serious illnesses, hospitalizations, and deaths. The pandemic also demonstrated variable mortality rates among people from different geographical regions. This was evident from the results of a previous study that showed higher mortality rates in the developed territories of the world including the Americas and European countries and comparatively low mortality rates in developing nations including India [1].

Although some research studies pointed to extreme-aged populations in developed countries as the reason for high mortality rates, additional research in this direction could improve the understanding of the causes of variable mortality rates. We hypothesize and explore the possibility of previous exposure to bat urine and feces contaminated with coronaviruses (CoVs) influencing COVID-19 outcomes.

2. Current Knowledge on the Research Topic

The current novel SARS-CoV-2, responsible for the COVID-19 pandemic has been noted to share genomic similarities with previous SARS-CoV (79%) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (50%) discovered in 2002 (China) and 2012 (Saudi Arabia), respectively [2]. Moreover, CoVs and other viruses have been frequently identified in bats. Further, the ability of bats to travel to different geographical regions facilitates the relocation of the microbes they carry to other areas. Besides, the microbes jump from one host to another, adjusting to varying hosts by developing mutations and transforming into a hitherto novel microbial species [3]. (Figure 1)

Image credit: Venkataramana Kandi

Historically, the human race has been experiencing epidemics (affecting thousands of people within a country) and pandemics (affecting millions of people involving multiple countries) caused by different microbial species resulting in millions of deaths. The microbes involved included the smallpox virus and *Influenza* virus. Particularly, *Influenza* viral pandemics have been on the rise since the initial parts of the 20th century with the emergence of the Spanish flu in 1918. Despite their ubiquitous nature, the *Influenza* virus with its ability to undergo mutations jumps from one host to the other, mixing with related viruses, and emerges as a novel species not known to exist previously.

The novel viruses that are previously unknown when encountered by humans result in severe forms of the disease. This is due to the failure of the immune system to recognize the microbe, causing immunological unresponsiveness and hyperreactivity. The immunological unresponsiveness contributes to severe and more invasive infections and adverse clinical outcomes. The immunological hyperreactivity due to infection with novel microbes damages the host tissues, causing organ dysfunction and death.

The reasons for the variable effects of the SARS-CoV-2 pandemic, especially in terms of morbidity and mortality are not completely understood. Current evidence suggests that the clinical outcomes of COVID-19 depend on factors like individuals' immune system, vaccination, age, sex, co-morbidities, and other factors [4,5,6]. It is important to explore the possibilities of previous exposures to bat urine and feces contaminated with CoVs and its influence on clinical outcomes through extensive research.

3. Available Evidence on the Research Topic

Since the present and previous CoVs have genetic similarities, the possibility of exposure to bat CoVs enabling the human immune system to recognize and react during future exposures to similar microbes needs to be investigated.

Urbanization and industrialization may have disturbed the bat ecosystem. This could contribute to disturbances in the bat habitats. Bats generally live away from human residences, in underground caves and tall trees deep inside the jungles. However, due to increasing human invasion, bats have been noted to live close to human habitats, breeding in the small holes and spaces inside concrete buildings. This causes exposure of humans to bat body fluids including their saliva, urine, and feces. Since bats are known carriers of hundreds of species of microbes including the CoVs, the chance of humans encountering them increases [7,8]. (Figure 2)

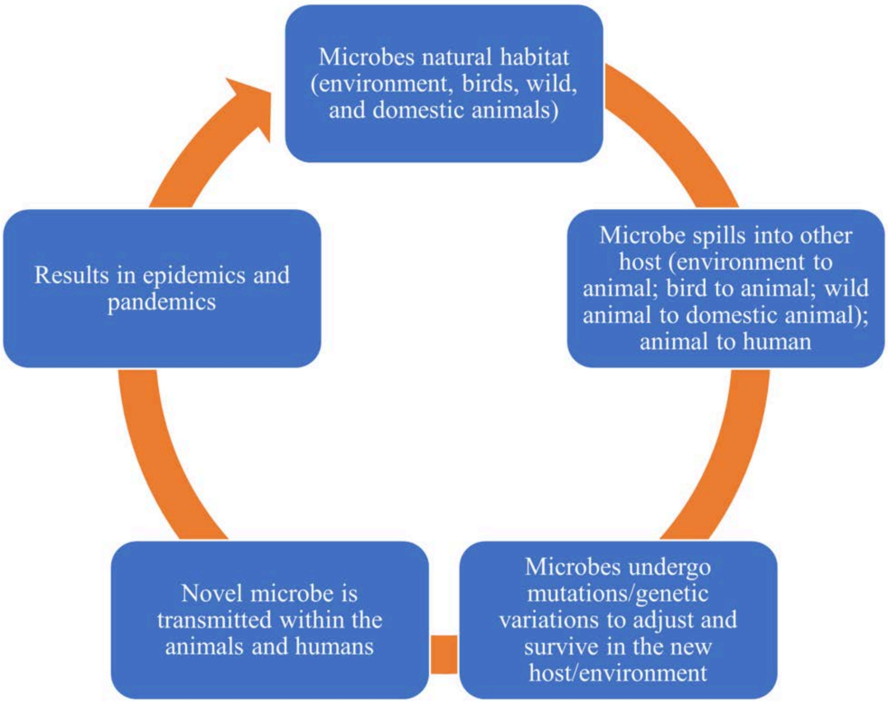

Figure 1. Potential mechanism behind the evolution of a novel microbial species

Figure 2. Image showing human intrusion into bat habitats and bat intrusion into human habitats

Image credit: Venkataramana Kandi

A: Human invasion into the deep jungles where bats live; B: Bats inhabiting human houses and breed; C: Bats droppings and body fluids inside a building

It has been confirmed that bats are colonized with hundreds of microbes, mostly viruses, including the CoVs, the *Nipah* virus, the *Ebola* virus, the *Marburg* virus, and the *Rabies* virus. Bat seroprevalence studies revealed antibodies against viruses like the Nipah [9].

Previous studies on the colonization of viruses were performed among bats collected from deep forests in India. The rectal and throat swabs were screened for evidence of viral nucleic acid. All the throat swabs were negative for viral ribonucleic acid (RNA) but the rectal swabs from Kerala (5.53%), Himachal Pradesh (6.89%), Puducherry (26.09%), and Tamil Nadu (4.13%) were positive for coronavirus nucleic acid. No proof of coronavirus nucleic acid was found in bats screened from Karnataka, Chandigarh, Gujarat, Odisha, Punjab, and Telangana [10].

Interestingly, bats do not affect the viruses carried by them. Additionally, most viruses identified in bats were associated with animals, signifying their importance in causing zoonotic infections [11]. It can be hypothesized that bats could feed on both wild and domestic animals. This may result in the transmission of the virus from bats to animals and vice versa.

Furthermore, bats were noted to carry many bacterial species (*Escherichia coli*, *Klebsiella*, *Staphylococcus*, and others) including multi-drug resistant ones [12]. It is, therefore, important to understand the microbial diversity of bat species dwelling not only in the deep forests but also those residing close to human habitats.

A previous study investigated and found *Nipah* virus in the urine samples of bats collected from the 20-kilometer range of the outbreak region in Bangladesh after a few weeks of the outbreak [13]. This study reaffirms the importance of microbial shedding in bat body fluids including the urine. Such studies are essential to understanding microbial diversity and the potential for microbial dissemination through bat urine and feces.

There could be different reasons for the variable mortality rates observed during the initial phase of the COVID-19 pandemic. Interestingly, states like Delhi, Gujarat, West Bengal, Telangana, Maharashtra, and Madhya Pradesh reported higher death rates, when compared to other states. Lower mortality rates were noted in Tamil Nadu, Andhra Pradesh, and Karnataka, among others [14].

It may be noted that some states with high mortality rates like Telangana and Gujarat revealed no evidence of CoVs in the bats as observed in the previous study. Further, states with low mortality rates like Tamil Nadu showed evidence of CoVs in the bat species [10].

4. Working Hypothesis

The available data suggests people living in areas where bats are known to carry CoVs could get exposed to the virus through bat body fluids, urine and feces. This may have introduced the microbe to their immune system. Therefore, these individuals could have mounted a better immune response after encountering SARS-CoV-2. Similarly, people not exposed to CoVs before the pandemic may have responded to the infection differently. (Figure 3)

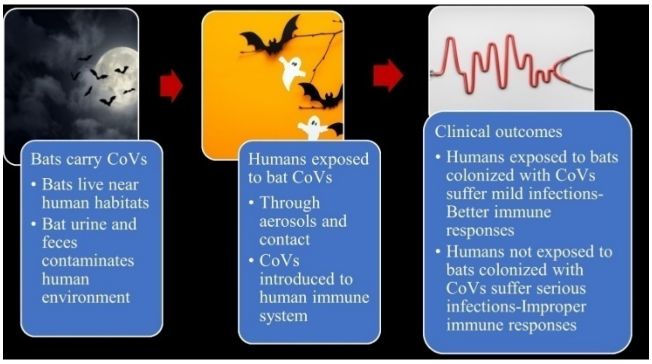

Figure 3. The influence of bat coronavirus exposure on COVID-19 clinical outcome

Image credit: Venkataramana Kandi

5. Debate About the Proposed Hypothesis

The study is primarily based on a hypothesis, drawing on previous research about bat coronaviruses. However, no direct evidence links prior exposure to bat excreta with immune responses to SARS-CoV-2.

Author argument: Yes, this hypothesis serves as a template and provides a new dimension to research with reference to COVID-19 caused by the SARS-CoV-2. **While the hypothesis is compelling, the manuscript does not sufficiently explain how exposure to bat urine and feces would lead to a specific immune advantage or disadvantage to SARS-CoV-2.**

Author argument: Further experimental research, such as serological tests on populations exposed to bats and analysis of bat CoVs and human immune responses, is required to substantiate these claims.

The manuscript also tends to overgeneralize findings from unrelated studies. For instance, references to zoonotic diseases like Nipah or Ebola are intriguing but may not directly support the mechanism being proposed for SARS-CoV-2.

Author argument: History has been a witness to several microbial diseases that resulted in the deaths of millions of people. For example, the smallpox caused by the *Variola* virus (VARV) infections in humans caused the death of persons leaving the survivors to develop lifetime immunity against reinfections. The same phenomenon was evident with other infectious diseases like chickenpox caused by the *Varicella Zoster Virus* (VZV) and the *Influenza* viruses. Furthermore, the world has been witnessing extremely few incidences of COVID-19. This does not mean the causative virus has been eliminated, but people could have developed some immunological protection owing to natural exposures to the virus and vaccination. The same may be implicated with the *Nipah* virus, also transmitted through bats. There is a possibility that exposure to bats carrying this virus may provide immunity. However, to support this inference, the bats must be screened for the virus and serological evidence of ant-*Nipah* virus antibodies in the bats, humans, and animals is required. Furthermore, the re-emergence of mpox disease caused by the *Mpox* virus affecting humans has been attributed to the waning immunity against pox viruses, especially the VARV [15].

The manuscript lacks adequate references to support some of its key claims, particularly regarding prior exposure to bat coronaviruses. More citations from relevant studies would strengthen the arguments.

Authors argument: The available literature may be inadequate to confirm the relationship of prior exposure to bat colonization with microbes conferring immunological protection against infection/severe disease. However, this hypothesis potentially paves the way for further research studies to understand this phenomenon about many current and potentially emerging and re-emerging microorganisms.

6. Plan for Further Research and Implementation

The available literature and the observations from past experiences suggest human exposure to bat CoVs could have influenced COVID-19 outcomes. However, this inference needs to be supported by an increased understanding of the colonization of bat species with CoVs, and their genetic similarities with CoVs causing human and animal infections in different geographical regions. Particularly, intensified research is needed to evaluate the bats residing close to human habitats for their colonization of CoVs. Furthermore, seroprevalence studies in bats, animals, and humans could improve understanding of the Coronavirus exposures in respective species.

7. Conclusions

The COVID-19 pandemic contributed to severe morbidity and mortality in people throughout the world. Despite the availability of improved healthcare facilities and technological advances compared to the previous century, the global population was severely affected by the COVID-19 pandemic. Moreover, people have been experiencing post-COVID-19 complications affecting their quality of life. The causative agent of COVID-19, the novel SARS-CoV-2, was presumed to have evolved from bats. Since bats carry several CoVs, it is essential to understand the bat colonization of microbes and their implications for human disease and its outcomes. Effective screening of bats near human habitats for colonizing microbes could be instrumental in predicting and preventing future pandemic-like situations. Moreover, seroprevalence studies in bats, humans, and animals could improve the understanding of previous exposures to CoVs and their potential role in immunity and disease outcomes.

List of Abbreviations

COVID-19: Coronavirus disease 2019
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
SARS-CoV: Severe acute respiratory syndrome coronavirus
MERS-CoV: Middle east respiratory syndrome coronavirus
CoVs: Coronaviruses
ICU: Intensive care unit
VARV: Variola virus
VZV: Varicella Zoster virus

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