Emerging pandemics and the role of bats

Frank Gaglioti
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Many viral infections that plague humans originate from bats, yet intriguingly, bats suffer no ill effects from the myriad viruses that inhabit their bodies. Scientists are researching how this occurs in the hope of finding some insights into how to control or moderate the impacts of viral infections on humans.

Earlier this year, zoologist and geneticist Emma Teeling from University College Dublin told the *Guardian*, "Bats have the potential to teach us a great deal about how to fight off disease."

Bats are a unique order of mammals, consisting of over 1,400 species known to exist on every continent except Antarctica. They range in size from the Kitti's hog-nosed bat at 29 mm to species of fruit bat that are 40 cm long with a 1.5 m wingspan. They have a relatively long lifespan, with some species known to have lived approximately 40 years, far longer than most small animal species. They are the only mammal to have evolved flight and the ability to navigate through echolocation. Bats evolved in the time of the Eocene Epoch about 56 to 33.9 million years ago.

Bats are the second largest mammal order, comprising 22 percent of all named species of mammals. Only the rodent order outnumbers them.

SARS-CoV-2, the coronavirus causing the ongoing COVID-19 pandemic that has killed at least 26 million people, is thought to have originated from bats. A study published in September 2021 outlined the discovery in 2020 by French and Laotian scientists of three coronaviruses considered to be close relatives of SARS-CoV-2 in bats living in limestone caves in Laos. This was a devastating blow to the Wuhan lab theory of the origin of the virus. The discovery confirmed the zoonotic origin of the virus as is the case for all other known viruses.

Many other viral infections are known to have originated from bats. In an important review published in *Nature Reviews Microbiology* in June 2020, molecular virologist Michael Letko and his team at the National Institute of Allergy and Infectious Diseases in Hamilton, Montana, commented:

> Most viral pathogens in humans have animal origins and arose through cross-species transmission. Over the past 50 years, several viruses, including Ebola virus, Marburg virus, Nipah virus, Hendra virus, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory coronavirus (MERS-CoV) and SARS-CoV-2, have been linked back to various bat species.

Letko et al. continued:

> Despite decades of research into bats and the pathogens they carry, the fields of bat virus ecology and molecular biology are still nascent, with many questions largely unexplored, thus hindering our ability to anticipate and prepare for the next viral outbreak.

Bats have been identified as repositories for Marburg virus, Hendra virus, Sosuga virus and Nipah virus. African fruit bats are thought to be the source of the Ebola virus.

Many coronaviruses are considered to have emerged from bats, including severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory coronavirus (MERS-CoV). Bats are responsible for several emergent coronaviruses such as Swine acute diarrhoea syndrome coronavirus, which emerged from horseshoe bats.

The role that bats play in the zoonotic spillover of emerging viral diseases and possible pandemics is exacerbated by the impacts of poverty, as people are forced to rely on bush meat to survive, increasing the chance of infections. Poor communities clearing land for agriculture disturb animal habitats, creating opportunities for zoonotic spillover of new viral diseases.

Bats rarely directly infect humans, but this usually occurs through an intermediary species such as civets for SARS-CoV and camels for MERS-CoV. As humans mostly become infected through a secondary agent, this means it is very difficult to determine the original source of a given virus, many of which are extremely dangerous. MERS-CoV has a lethality rate of 35 percent while Marburg is up to 90 percent.

Marburg virus

Marburg is a relatively recent emerging viral infection. It was first identified in 1967 in simultaneous outbreaks in Marburg and Hamburg in Germany, as well as Belgrade in the former Yugoslavia. The outbreak started with laboratory workers who became infected from African green monkeys. It resulted in 31 people being infected, of whom seven died, with a fatality rate of 23 percent.

Most other outbreaks of the virus have been confined to Africa, with the largest in the Congo and Angola in 1998-2000 and 2004-05, respectively. The Congo outbreak infected 154 people resulting in 128 deaths, while the Angolan outbreak infected 252 people with 227 deaths, fatality rates of 83 and 90 percent, respectively. The Angolan fatality rate was the highest on record for this type of virus.

The latest outbreaks were in Equatorial Guinea and Tanzania that were declared on January 13 and March 16, 2023, respectively. In the Equatorial Guinea outbreak there were 20 probable cases resulting in seven deaths, while in Tanzania there were nine cases resulting in six deaths.

Two viruses have been identified that cause Marburg viral infections: the Marburg virus and the Ravn virus, both of which are similar to the Ebola virus. These viruses are members of the Filoviridae family of virus that consist of a single strand of ribonucleic acid (RNA).

Marburg virus is considered so lethal that the World Health Organisation (WHO) has characterised it as a Biosafety Level 4, the highest security rating, in line with its high lethality and transmissibility. Marburg and the Ebola virus are regarded as some of the deadliest viruses

known to infect humans.

Marburg virus has been found in Egyptian rousette bats (Rousettus aegyptiacus), a type of fruit bat found in Africa, the Middle East, the Mediterranean and the Indian subcontinent. People become infected due to prolonged exposure to bat urine or saliva in caves and abandoned mines, where the bats are known to roost in large colonies. Healthcare workers have been infected due to treating infected patients.

Marburg virus can be transmitted from human-to-human through contact with bodily fluids. It has an incubation period of 2-21 days. Early symptoms are similar to influenza, including high fever, chills, severe headache, severe tiredness and muscle aches and pains.

The infection then becomes more acute, with severe diarrhoea, abdominal pain and cramping, nausea and vomiting. The WHO describes the infected person at this stage as "showing 'ghost-like' drawn features, deep-set eyes, expressionless faces, and extreme lethargy."

The severest cases have some form of bleeding, often from several orifices. The person often dies eight to nine days after the onset of symptoms.

In an important study published in *Nature Communications* in January 2020, titled "Isolation of Angola-like Marburg virus from Egyptian rousette bats from West Africa," disease ecologist from the US Centers for Disease Control and Prevention (CDC) Brian R. Amman and his team outlined that the virus causing the Angolan Marburg outbreak was a significantly more virulent strain of the virus.

The study pointed out that the Angolan outbreak was the only one to have occurred in East Africa, indicating the further spread of the virus.

"All previous MVD (Marburg virus) outbreaks occurred in, or originated from, Uganda, Kenya, Democratic Republic of the Congo (DRC), or South Africa ex Zimbabwe," the authors stated.

East Africa is known as a place of large concentration of Filoviridae virus. Amman et al. commented that "Other filoviruses circulating in Africa include the marburgvirus, Ravn virus (RAVV), as well as five ebolaviruses, EBOV, Sudan virus (SUDV), Tai Forest virus (TAFV), Bundibugyo virus (BDBV), and the recently discovered Bombali virus (BOMV)."

The Sudan virus occurs in the Sudan, Tai Forest in the Ivory Coast, Bundibugyo and Bombali in Sierra Leone.

Potential for Marburg to become a pandemic

While the Marburg virus is spread through direct contact with infected bodily fluids from bats, secondary animal vectors such as apes, or infected humans, there is the potential for the virus to mutate so it can spread through aerosol transmission. Such an outcome could have devastating consequences, as the virus would have the potential to develop into a pandemic. The evolution of a constant stream of SARS-CoV-2 variants starkly demonstrates the potential for RNA viruses to mutate very rapidly.

Marburg mostly occurs in Africa but there have been two outbreaks in other countries, highlighting the ability of the virus to spread more broadly. In 1990, a laboratory worker in the Soviet Union became infected due to contact with infected tissue while containing the virus. The infected person did not die. In July 2008, a Dutch tourist who had visited caves in Uganda inadvertently brought Marburg virus to the Netherlands. The infected person died but the virus did not spread as the victim was isolated in time.

An important review article by virologist Sophie J. Smithers of the Defence Science and Technology Laboratory in the UK, published in the journal *Viruses* in April 2022, examined the "aerosol survival comparison" of the Ebola and Marburg viruses.

The review stated, "This work will help inform on the relative aero stability and virulence of different variants and isolates. Studying aerosols is important due to the possibility of deliberate or accidental release or generation of aerosolized virus."

Smithers and her team point out that the Ebola and Marburg viruses are evolving constantly, producing new variants and that "infection of animals including non-human primates via the aerosol route is possible in laboratory studies."

"Each outbreak of EBOV or MARV is typically associated with the emergence of a different variant and multiple isolates with the result that many variants and isolates exist," Smithers et al. stated.

It is completely possible that a new Marburg variant could evolve to transmit via aerosols, developing into a pandemic involving a far deadlier virus than SARS-CoV-2.

Bats and viruses

The fact that bats are known to harbour myriad different viruses, but can coexist without any ill effect on the host, has become a promising area of research with potential insights into ways of protecting humans from viral infections.

"There is a kind of peace treaty between bats and the pathogens they host," virologist Joshua Hayward of the Burnet Institute in Melbourne, Australia, told *Nature*.

Evidence is emerging that it is bats' long coexistence with virus species that makes any zoonotic spillover so lethal to humans.

A fascinating study by virologist Cara Brook and her colleagues at the Department of Integrative Biology at UC Berkeley in California, published in February 2020 in *eLife*, explains that bats have a "hyper-vigilant immune response" that would cause dangerous inflammation in other mammals.

The authors state:

> Bats, however, have adapted anti-inflammatory traits that protect them from such harm, include the loss of certain genes that normally promote inflammation. However, no one has previously explored how these unique antiviral defenses of bats impact the viruses themselves.

Brook and her team used laboratory cell lines from the black flying fox (Pteropus Alecto) in which its interferon pathway is always on. This means its immune system is constantly and "perpetually trying to fight viruses." They also studied the Egyptian fruit bat (Rousettus aegyptiacus) in which the pathway goes on only during infection. They compared the response of the bat cells to those of African Green Monkeys (Chlorocebus aethiops).

Interferons are signalling proteins made in a cell in response to viral infection to fight an invasion. The bat and monkey cell lines were infected with Ebola and Marburg. The monkey cells were completely destroyed by the viruses but some of the bat cells survived.

The researchers replicated the experiment using mathematical modelling to determine how fast the viruses infected other cells and whether antiviral defences played a role in their spread. The modelling found that the viruses replicated under pressure from the bats' immune system spread rapidly from cell to cell. The rapid spread helps the viruses counter the bats' antiviral abilities that quickly mounted defences. In the monkey cells, the viruses spread more slowly but all the cells were destroyed.

Brook and her team noted:

> In both bat species, the strongest antiviral responses were countered by the virus spreading more quickly from cell to cell. This suggests that bat immune defences may drive the evolution of faster transmitting viruses, and while bats are well protected from the harmful effects of their own prolific viruses, other creatures like humans are not.

Scientists consider bats' ability to dampen their inflammatory response to viral infection important in their ability to coexist with viruses. One mechanism that is being actively researched is that this characteristic is connected to bats' ability to fly. Due to this ability, bats have an elevated metabolic rate, but in spite of this they have a relatively long lifespan, an observation which has triggered considerable interest.

An important study by Matae Ahn and his team from Duke–NUS Medical School in Singapore published in *Nature Microbiology* noted:

> As the only flying mammal, bats endure high metabolic rates yet exhibit elongated lifespans. It is currently unclear whether these unique features are interlinked. The important inflammasome sensor, NLR family pyrin domain containing 3 (NLRP3), has been linked to both viral-induced and age-related inflammation. Here, we report significantly dampened activation of the NLRP3 inflammasome in bat primary immune cells compared to human or mouse counterparts.

Inflammasome is an important cell signalling process that regulates the production of cytokine and is essential for the immune system. NLRP3 inflammasome is a multi-protein complex that plays a pivotal role in regulating the immune system.

The report notes that "how bats limit excessive inflammation while asymptomatically hosting a greater variety of viruses is unknown."

A great deal of work had concentrated on the NLR family pyrin domain that recognises cellular stresses. The study reports a mechanism in bats that dampens the inflammation response to three RNA viruses, without affecting the viral loads in primary immune cells. They found dampened transcriptional priming and a lower functional capacity of bat NLRP3. This was in response to exposure to the bat-borne Melaka virus and MERS coronavirus. These viruses induced inflammation in human and mouse cells.

"Bats have naturally dampened stress-related and virus-induced host inflammatory responses, with implications for longevity and asymptomatic viral reservoir status," Ahn et al stated.

In order to expand our understanding of bats, Professor Emma Teeling, the head of the Laboratory of Molecular Evolution and Mammalian Phylogenetics at the University College Dublin, founded the Bat1K project in 2017 that aims to map the genome of all bat species. This will provide invaluable insights into bat biology and their unique ability to live with viruses.

"If we could mimic the immune response of bats to viruses, that allows them to tolerate them, then you could look to nature to find a cure," Teeling told the BBC. "It's already evolved, we don't need to reinvent the wheel. We now have the tools to be able to understand the steps we need to take; we need to develop the drugs to do it."

In this context, the political attacks that have been made throughout the COVID-19 pandemic against principled scientists studying these topics and the dangers of future spillover events, including Drs. Peter Daszak, Shi Zhengli, Kristian Andersen, Peter Hotez, and many more, are all the more deplorable.

The pandemic has revealed the underlying antagonism between the capitalist profit system, riven by divisions between nation-states, and the ability of scientists to carry out their research unhindered. The full development of science and the capacities of mankind to understand nature, prevent future pandemics and guarantee a high quality of life to all, requires the building of an international socialist economy based on human needs, not private profit.