Microbial Biotechnology

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From Bat to Worse: The Pivotal Role of Bats for Viral Zoonosis

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Received: 12 June 2025 | **Accepted:** 19 June 2025

Funding: The author received no specific funding for this work.

Keywords: Chiroptera bat | coronavirus | emerging infectious diseases | innate immunity | lyssavirus | Marburg virus | Nipah virus | zoonosis

ABSTRACT

Zoonotic infections are increasingly observed and bats (Chiroptera) are playing a pivotal role here. The causal chain of events has been elucidated for Henipavirus (family: paramyxoviruses) infections. Deforestation combined with climate change has reduced the food sources of Pteropus fruit bats and attracted them to fruit trees planted around piggeries in Malaysia, transmitting Nipah virus to pigs as amplifying hosts and then to pig farmers and abattoir workers. Similar scenarios were seen in Australia where Pteropus bats transmitted Hendra virus to horses as intermediate hosts for human infections. Pteropus bats contaminated palm sap collected in Bangladesh with Nipah virus where fatal human-to-human transmissions occurred annually. Less direct evidence links coronaviruses carried by Rhinolophus bats with SARS and COVID-19 pandemics and a piglet epidemic in China. Rousettus bats living in caves transmitted the Marburg virus (family: filovirus) to miners in Africa. Most cases of human rabies in North America were caused by bat lyssaviruses (family: Rhabdoviruses). Bats are viral reservoir species for various virus families (reovirus, Hepacivirus of Flavivirus family, influenza A viruses). Bats are the only flying mammals which opened enormous evolutionary possibilities resulting in a worldwide radiation with 1400 species. Some bat species are represented by huge populations that come together in extremely crowded resting places that are conducive to viral transmission. Bats have evolved mechanisms that tolerate virus replication but suppress the associated pathology, making them healthy carriers for many viruses. It is speculated that with that strategy bats avoid an arms race with viruses for resistance and anti-resistance mechanisms. The excretion of viruses that are highly pathogenic for other mammalian orders could be used as biological weapons to defend their habitat against intrusion by mammalian competitors, including humans. This hypothesis might explain the increasing involvement of bat viruses in emerging infectious diseases observed in recent decades and expected in the future.

Viral epidemics are increasingly observed in the 21st century. Viral zoonosis plays a major role in emerging infectious diseases, and bats (mammalian order of Chiroptera) are likely sources for many of these outbreaks. The current Lilliput editorial review provides an overview of outbreaks with proven or suspected links to bat viruses, compiles data where bats are reservoir species for viral pathogens and asks the question: what bat traits underlie this peculiar pivotal role of bats for emerging infections?

1 | Anatomy of a Viral Zoonosis With Proven Links to Bat Viruses: Henipavirus Infections

With two emerging diseases caused by Nipah virus (NiV) and Hendra virus (HeV) which form the *Henipavirus* genus in the *Paramyxoviridae* family, we have reliable data on the origin of the viruses, and we have a basic understanding of the factors that led to these zoonosis events. With respect to case numbers,

NiV and even less HeV infections cannot be compared with the impact of the COVID-19 pandemic. However, the viral origin of the COVID-19 pandemic is still not clear and therefore allows a less clear illustration of basic principles. The World Health Organization has listed NiV in its R&D Blueprint as one of the 10 highest-priority pathogens (World Health Organization 2018) and NiV infections merit our attention not only for their high case fatality rates.

1.1 | The Search for the Viral Reservoir

The first human NiV cases were reported in pig farmers from Malaysia in late September 1998. The human NiV cases were associated with an outbreak of respiratory illness in pigs (Chua et al. 1999). By February 1999, the disease had spread to other areas of Malaysia and was linked to the transport of infected pigs. In March 1999, NiV cases were also observed in abattoir workers from Singapore who had handled infected pigs imported from Malaysia. The culling of more than 1 million pigs in Malaysia stopped the NiV outbreak which caused 265 cases of encephalitis and 105 deaths in Malaysia. The etiological agent was rapidly identified. Cerebrospinal fluid from fatal NiV cases induced characteristic cytopathic effects in Vero cells, and viral particles typical for paramyxoviruses were observed (Chua et al. 2000). The isolated virus was neutralised by HeV antiserum. However, sequencing of the NiV genome showed more than 20% sequence diversity from HeV, suggesting a distinct viral species. HeV had been traced to fruit bats in Australia, where fruit bats infected horses and caused a handful of fatal infections in humans who had close contact with horses. In the NiV outbreak area of Malaysia, serological surveys showed NiV antibodies in sera of most pigs and in the sera of few cats, dogs and bats in the outbreak area. However, no virus could be isolated and no viral RNA was detected in more than 300 analysed bats. The reservoir species for NiV remained thus undefined.

Subsequently, virologists collected sera from fruit bats and insectivorous bats from different areas in Malaysia as well as sera from wild boars, domesticated dogs and rodents around the outbreak areas. Overall, more than 300 bats representing 14 bat species were captured. Neutralising antibodies to NiV were detected in 31% of *Pteropus hypomelanus* and 17% of *Pteropus vampyrus* (Figure 1), two fruit bat species belonging to the Chiroptera suborder Megachiroptera (traditional taxonomy) or Yinpterochiroptera (new taxonomy), and with less than 5% seroprevalence in three further bat species. All other mammalian sera were negative. However, still no NiV could be isolated from bats (Yob et al. 2001). NiV-neutralising antibodies were also identified in other bat species (*Pteropus lylei*, *Rousettus leschenaultia*) from Cambodia and Vietnam, respectively. Serological characteristics suggested that viruses related to, but distinct from NiV, were widely circulating in Southeast Asia (Olson et al. 2002; Hasebe et al. 2012).

It needed much effort to provide direct evidence for NiV infection in bats: among 860 *P. lylei* bats in Thailand 9% showed NiV antibodies while only 1 and 6 animals, respectively, showed NiV RNA in saliva and urine (Wacharapluesadee et al. 2005).

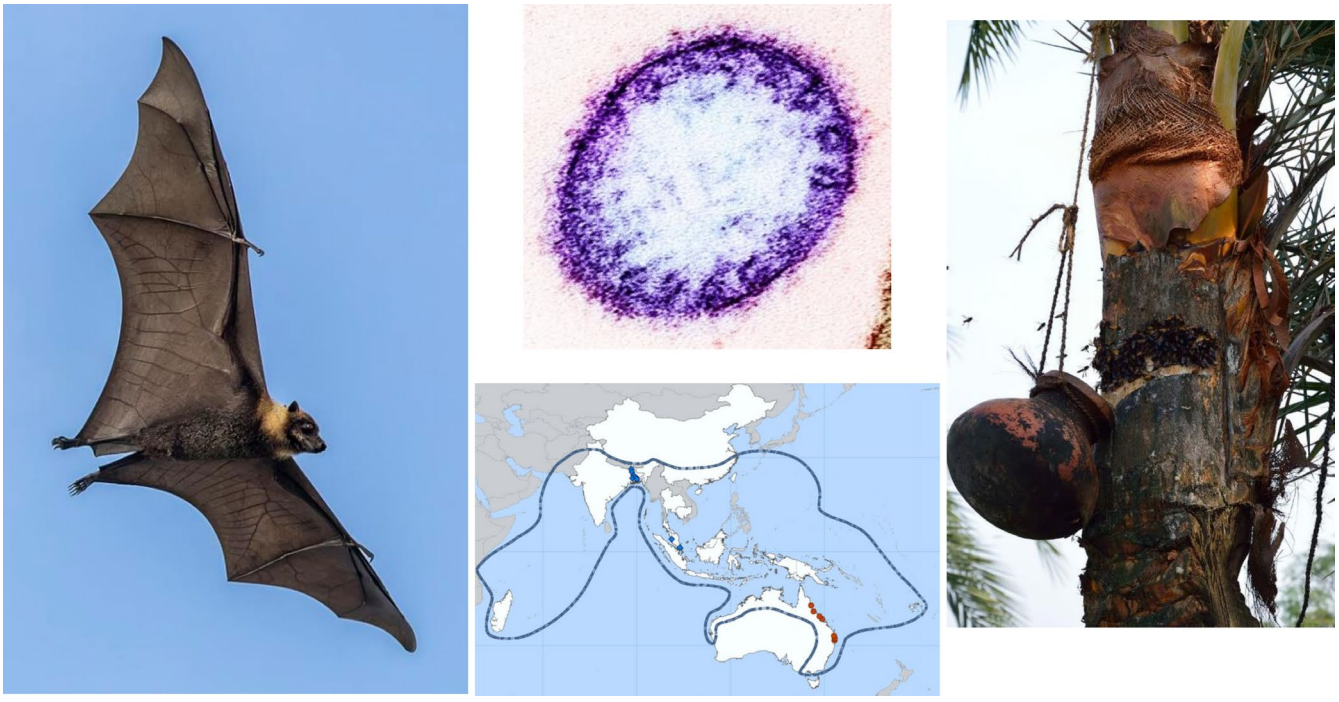

FIGURE 1 | Bat and Henipaviruses. Left: A Pteropus spec fruit bat in flight; Centre, top: Electron microscopy of Nipah Virus in false colour; Centre, bottom: Distribution map of *Pteropus* bats (blue broken line), blue diamonds: Human Nipah virus infections, orange diamonds: Horse/human Hendra virus infections, white-shaded countries: Countries with Henipavirus seropositive *Pteropus* bats; Right: Jar on a palm tree for sap collection in Bangladesh (figure credits: Left: Wikipedia Pteropus Charles Sharp; centre top: Wikipedia Nipah virus NIAID; centre bottom: Wikipedia Nipah virus CDC; right: Wikipedia Pteropus Biswarup Ganguly).

Likewise, among 140 bats investigated in India, only one *Pteropus giganteus* bat showed a low level of NiV RNA in the liver. Notably, the sequenced viral RNA was identical to that of NiV isolated from patients in India and Bangladesh and shared 96% identity with viruses from NiV patients and bats in Malaysia (Yadav et al. 2012). In Malaysia, it took three field surveys to isolate a NiV from two urine samples of *P. hypomelanus* and from a fruit partially eaten by bats. These viral RNAs shared 99% sequence identity with that of human NiV from Malaysia. The high sequence identity suggested that the spillover of NiV from *Pteropus* bats to humans was a recent event (Chua, Chua, and Wang 2002; Chua, Koh, et al. 2002). When testing nearly 3000 urine and throat samples from *Pteropus medius* and *R. leschenaultia* from Bangladesh, 11 NiV isolates were obtained. The genome sequences shared 99.9% identity with NiV from bat colonies separated by 350 km, suggesting viral dispersal by bat movements (Anderson et al. 2019). A NiV from *P. lylei* was isolated in Cambodia that shared 97.7% nucleotide sequence identity with human NiV isolates from Malaysia and lesser identity with NiV from Bangladesh, demonstrating some NiV strain differentiation. This bat isolate replicated to high viral RNA copy numbers in human and to lower copy numbers in bat cell lines. The isolate induced paralysis, breathing problems and prostration in experimentally infected hamsters and 100% lethality after a week (Gaudino et al. 2020).

1.2 | Push Factors

With the bat origin of NiV now demonstrated, Malaysian researchers looked for factors that might have precipitated the 1998 NiV epidemic. They identified a number of stress factors that affected the Malayan fruit bat population. They noted an encroachment of humans into the forest habitats of fruit bats by two decades of anthropogenic deforestation for pulpwood and industrial plantation. In addition, a drought driven by the severe 1997–1998 El Niño Southern Oscillation (ENSO) event reduced fruit and flower production in Malaysia. Finally, slash-and-burn deforestation in Sumatra and Borneo for oil palm plantations destroyed approximately 5 million ha of forest. With the prevailing southwesterly winds, these fires created the most severe haze ever known in Malaysia. The haze caused solar light extinction that reduced forest and agriculture productivity, which translated into starvation for fruit bats (Chua, Chua, and Wang 2002; Chua, Koh, et al. 2002). The link between deforestation/climate change and virus spillover by *Pteropus* bats has been convincingly demonstrated for HeV infections of horses in Australia (Eby et al. 2023). In Australia, *Pteropus* bats primarily feed on nectar, and the bats track ephemeral pulses of flowering *Eucalyptus* trees over hundreds of kilometres. When trees that provide food in winter do not flower because of variations in temperature and rainfall, *Pteropus* bats experience brief periods of food shortages to which they respond with behavioural changes (reducing roost sizes, searching for less nutritious alternative food sources). Deforestation for agriculture and urban spreading has reduced the habitat of *Pteropus* bats and, combined with ENSO events, induced starvation periods for the bats that were temporally associated with the HeV spillover infections. The physiological stress induced increased HeV excretion into the urine of bats (Becker et al. 2023).

1.3 | The Pull Factors

A viral reservoir in a wildlife species alone does not yet create a spillover infection in humans. Humans must come into close contact with the viral carrier species. This can occur with the intrusion of humans into the natural habitat of wildlife viral carriers. This might occur during deforestation activities or by bushmeat hunting, as demonstrated by a study from Cameroon (Pernet et al. 2014). The researchers investigated local serum collections from the fruit bat *Eidolon helvum* and from humans for neutralising antibodies to a NiV relative from an African bat. Half of the bats and 3% of the humans showed virus-neutralising antibodies. None of the humans without contact with bats displayed these antibodies. Bat bushmeat butchering increased the risk of a serologically diagnosed infection by 29-fold, while living in an area of deforestation already increased the risk of NiV seropositivity by tenfold.

An unfortunate agronomical advice created favourable conditions for a NiV spillover infection in Malaysia. To increase the small profit margin for pig farmers, agronomy experts suggested to combine animal husbandry with planting fruit trees. This dual farm use would provide an extra income from fruit and also provide shade to the pigs. Indeed, 100 ha of orchards surrounded the pig-farming area where the index human and pig NiV cases were reported in Malaysia (Chua, Chua, and Wang 2002; Chua, Koh, et al. 2002). *P. vampyrus* bats, normally absent in this area, were observed to visit orchards for foraging shortly before the outbreak. Partially eaten fruits were also found within pigsties, creating an infection chain connecting fruit bats with pigs as an intermediate amplifying host (which ate the fallen fruits contaminated by bat saliva) and the pig farmers. A combination of push and pull factors thus created the ground for a NiV spillover in Malaysia. Similar observations were made in Australia for HeV spillovers, where starving fruit bats were attracted to fruit and flower food sources in agricultural areas and in urban gardens (Plowright et al. 2011).

A strong pull factor also contributed to spillover infections with NiV in Bangladesh and India. NiV infections in these countries differed in epidemiological terms from those reported in Malaysia (Hossain et al. 2008). In the Muslim-majority country Bangladesh, pigs were excluded as intermediate amplifying hosts. In South Asia, human-to-human transmission was observed for those having close contact with the patients, particularly when caring for them. An early case–control study of a cluster of NiV cases in Bangladesh identified a strong pull factor. Drinking raw date palm sap, a popular and nutritious beverage in Bangladesh, was the only risk factor associated with the disease. Using cameras, the researchers identified the fruit bat *P. giganteus* drinking from the clay pots used to collect the sap at night, contaminating the sap with their urine (Luby et al. 2006). These researchers then compared 60 villages in Bangladesh reporting NiV cases with 147 control villages. They analysed ecological factors and human behavioural drivers for the geographic variation of NiV infection risk. As the sole difference, case villages showed a greater proportion of persons drinking palm sap (Luby et al. 2006). Human outbreaks occur almost annually in Bangladesh, and

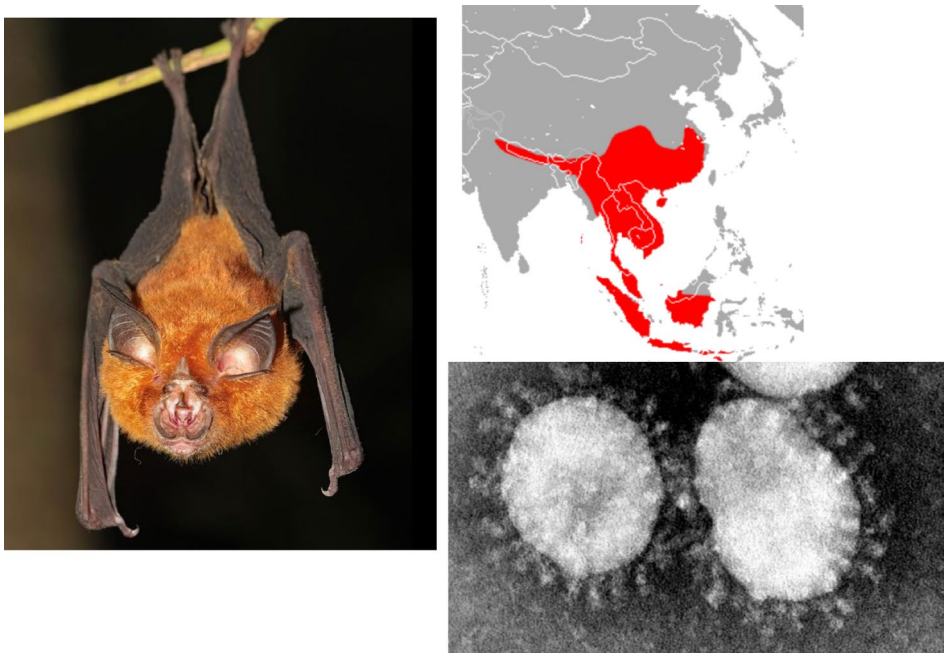

FIGURE 2 | Bat and coronaviruses. Left: A *Rhinolophus affinis* bat; Right, top: Distribution map of *R. affinis*; Right, bottom: Electron microscopy of a bat coronavirus (figure credits: Wikipedia Java Hufeisennase Ian Dugdale; right top: Wikipedia Java Hufeisennase IUCN Red List of Threatened Species; right bottom: Wikipedia SARS-CoV-2).

the seasonal timing of outbreaks coincides with patterns of raw date-palm-sap consumption in a region termed the 'Nipah belt'. Clinical cases and viral RNA detection in bats occurred when the *P. medius* bat population passed through troughs in the annual NiV antibody seroprevalence cycles, suggesting that viral spillover was linked to waning herd immunity in the bat population (Epstein et al. 2020). Due to land-use changes, forest cover in Bangladesh has decreased from 40% to less than 10%. As a consequence, *P. medius* has changed behaviour. The majority of *P. medius* populations are now small; they occupy roost sites for several years, live in areas of high human population density and opportunistically feed on cultivated food resources. This behavioural adaptation to environmental push and pull factors now favours viral spillover events (McKee et al. 2021). Climate change models predicted that the geographical range of *Pteropus* bats will extend beyond their currently occupied range (South and Southeast Asia) and potentially carry NiV to Arabia, Northern Australia and Africa (Daszak et al. 2013).

2 | Coronavirus Epidemics With Strongly Suspected Links to Bat Viruses: SARS, COVID-19 and SADS

2.1 | SARS-CoV-1

The 2002/2003 SARS-CoV-1 outbreak which started in Guangdong, China was first linked to the masked palm civet as a viral source. The civet was sold as a food delicacy at the live animal markets in Guangdong. However, experimental infections of palm civets with SARS-CoV-1 resulted in overt disease. In addition, no indications of a widespread infection in wild or farmed civets were detected, rendering them an unlikely viral reservoir species. In contrast, in 2004, when Chinese researchers collected blood, faecal and throat swabs from 400 bats in Guangdong and adjacent provinces, three *Rhinolophus* bat species (Figure 2), belonging to the bat suborder Microchiroptera, showed antibodies reacting with SARS-CoV-1 in ELISA (Li et al. 2005). The data demonstrated a seroprevalence ranging from 28% to 71% in the bat sera and PCR positivity for the nucleocapsid and polymerase gene of SARS-CoV-1 in 10%–12% of the faecal samples. No infectious virus could be isolated but the whole viral genome from one faecal sample could be reconstituted. This bat coronavirus genome shared between 96% and 100% sequence identity with SARS-CoV-1 except for the S1 domain of the spike gene, which is the receptor-binding domain (RBD). Over this region, sequence identity was only 64%, which fits with the observation that the bat sera did not neutralise SARS-CoV-1. While the source for the 2002 SARS-CoV-1 outbreak was not identified, the data demonstrate that *Rhinolophus* bats are a viral reservoir species for SARS-CoV-1-like coronaviruses (SL-CoV). Subsequently, Chinese researchers analysed 117 anal swabs from *R. sinicus* bats from Yunnan province (Ge et al. 2013): 23% tested positive for coronavirus using a viral RNA-dependent RNA polymerase gene-specific PCR test; peak prevalence of 48% was observed in autumn compared to 7% in spring. Two viral bat genomes shared 95% overall nucleotide sequence identity with SARS-CoV-1 extending also over the receptor-binding region of the spike gene. The authors suggested that direct bat-to-human infection could be a plausible scenario for some bat SARS-like coronaviruses.

2.2 | SARS-CoV-2

The origin of SARS-CoV-2 causing the COVID-19 pandemic is still unclear. Major questions concern the animal reservoir for the SARS-CoV-2 strains (bats?), whether a passage in an intermediate host (pangolins? racoon dogs?) was needed to adapt the virus for human transmission, and whether the initial

transmission event to humans occurred in a live animal market or in a laboratory working with bat viruses. Despite these uncertainties, some observations link SARS-CoV-2 to bat viruses. Bats harbour the closest viral relatives of SARS-CoV-2 with respect to genomic identity. The report describing the first SARS-CoV-2 human isolates in January 2020 noted 96.2% nucleotide sequence identity over the entire genome with the *Rhinolophus affinis* bat coronavirus RaTG13, isolated in 2013 in China (Zhou et al. 2020). However, a drop in sequence identity was found over the RBD of the spike protein, resulting in a very limited affinity of RaTG13 to the human ACE2 receptor used by SARS-CoV-2, excluding RaTG13 as a direct precursor for SARS-CoV-2.

Coronaviruses are a frequent finding in bats. For example, when 645 bats caught in Laos were screened for coronaviruses, 24 individuals from 10 bat species tested positive in PCR (Temmam et al. 2022). Seven bats yielded a virus from the *Sarbecovirus* subgenus to which SARS-CoV-2 belongs; all bats belonged to *Rhinolophus* species. The Laotian *R. malayanus* BANAL-52 coronavirus shared 96.8% sequence identity with SARS-CoV-2 collected in 2019. Notably, these bat viruses differed by only one or two amino acid residues in the RBD of their spike proteins from SARS-CoV-2 and could mediate human ACE2 receptor-dependent entry and replication in human cells, which was inhibited by antibodies that neutralised SARS-CoV-2. However, none of these bat viruses contained a furin cleavage site in the spike protein, which is important for human-to-human transmission of SARS-CoV-2. Again, BANAL-52 is not the direct ancestor of SARS-CoV-2.

Sarbecoviruses undergo extensive genomic recombination. One might therefore not expect to find a direct ancestor of either SARS-CoV-1 or SARS-CoV-2 circulating in wild bats. To address this problem, a consortium of researchers conducted comparisons of non-recombinant subgenomic segments of sarbecoviruses (Pekar et al. 2025). They concluded that the closest-inferred bat virus ancestors of both SARS-CoV-1 and SARS-CoV-2 circulated in bats in the years immediately preceding the emergence of each pandemic virus. By performing phylogeographic analyses, they deduced that the precursors of SARS-CoV-1 and SARS-CoV-2 emerged in places far from where the SARS and COVID-19 pandemics started. To bridge this geographical gap, they postulated an intermediate animal host that sparked these zoonotic epidemics transported by wildlife trade.

2.3 | SADS

A veterinary coronavirus outbreak also provided evidence of a bat virus involvement. Chinese researchers reported in 2017 a large-scale outbreak of fatal disease in pigs which was called Swine acute diarrhoea syndrome (SADS), killing over 24,000 piglets on a farm in the Guangdong province (Zhou et al. 2018). Porcine epidemic diarrhoea virus, a coronavirus, that had caused prior outbreaks on this farm, could not be detected. Metagenome sequencing of the small intestine from a diseased piglet matched sequences of the bat coronavirus HKU2, which was isolated from Chinese horseshoe (*Rhinolophus*) bats in the Guangdong province. The overall genome identity between the pig outbreak strain, SADS-CoV, and the HKU2 from bats was 95%, but dropped to 86% over the spike gene S. From 600 anal swabs of bats captured in the Guangdong province, 10% tested positive for the pig outbreak strain with overall genome sequence identity ranging from 96% to 98%, which extended to the spike S gene. All positive samples were from *Rhinolophus* bats. Phylogenetic tree analysis showed that different *Rhinolophus* species contained distinct coronaviruses, the closest to the pig isolated coming from *R. affinis*. The authors concluded that bat coronaviruses also threaten veterinary health in animals of economic importance. In addition, they isolated a bat coronavirus WIV1 which could use the human ACE2 protein as an entry receptor. This observation suggested to them that direct bat-to-human infection is a plausible scenario for some bat SL-CoVs.

3 | Bat Virus Links With Human Filovirus Epidemics: Ebola and Marburg Virus

3.1 | Ebola Virus

Between 2002 and 2005, Ebola virus outbreaks occurred among humans in Gabon and Zaire. As chimpanzees and gorillas also suffered severe disease, they were not a likely virus reservoir species. To identify potential reservoirs, researchers captured more than 1000 local animals, including bats, birds and small terrestrial animals. Ebola virus-specific antibodies and Ebola virus RNA belonging to the Zaire clade were detected in liver and spleen samples of *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*, all Macrochiroptera fruit bats. Bats tended to be either seropositive or viral RNA positive, suggestive of recent infections in the latter cases. The affected human populations consumed fruit bats as bushmeat (Leroy et al. 2005). In a follow-up study, 1390 samples were collected from these three fruit bat species, and 40 bats were positive for Ebola virus antibody (Pourrut et al. 2007).

For the large Ebola outbreak in West Africa which led to 17,000 human cases and 6000 deaths in 2014, researchers conducted a 4-week field mission at the beginning of the outbreak. They captured 150 bats belonging to 13 species but all were negative for Ebola virus RNA (Marí Saéz et al. 2015). In a 2007 survey conducted in Ghana, about a third of different fruit bat species showed Ebola virus antibodies, nevertheless pointing to fruit bats as a potential reservoir for Ebola virus (Hayman et al. 2012).

3.2 | Marburg Virus

Liver and spleen samples from 1100 bats representing 10 distinct species from Gabon and the Democratic Republic of Congo (DRC) were investigated for Marburg virus RNA by RT-PCR. Four individuals of the fruit bat *Rousettus aegytiacus* (Figure 3), also a member of the Megachiroptera bat suborder, were positive, harbouring unique sequences from a single Marburg virus lineage. More than 400 bats were then investigated for the presence of Marburg virus-specific antibody: 29 individuals tested positive, all belonging to *R. aegyptiacus*, suggesting a 9% seroprevalence. All fruit bats with positive results were clinically healthy (Towner et al. 2007).

In 2007, miners working in the Kitaka Cave, Uganda, were diagnosed with Marburg haemorrhagic fever. The cave contained a colony of about 100,000 *R. aegytiacus* bats. In 2007, 5.6% of the

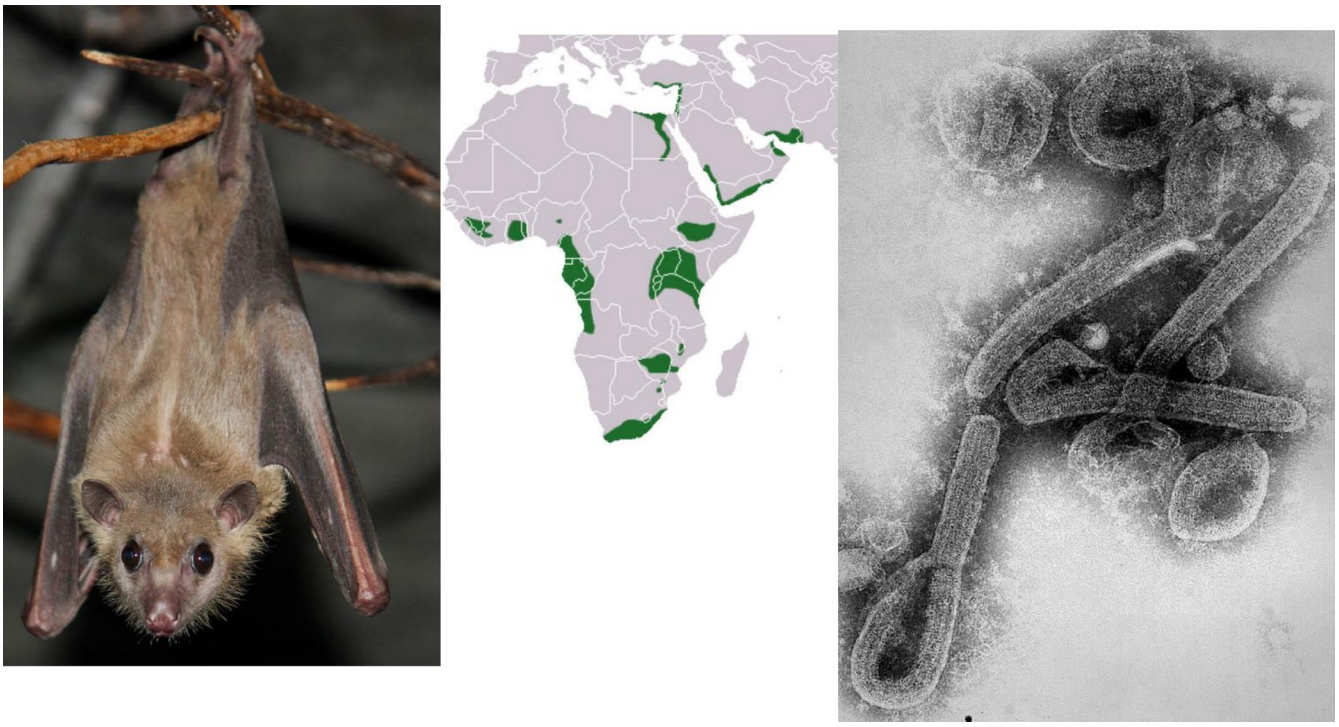

FIGURE 3 | Bat and Marburg virus (filovirus). Left: A *Rousettus aegyptiacus* bat; Centre: A distribution map of *R. aegyptiacus*; Right: EM of Marburg virus. (figure credits: Left: Wikipedia Nilflughund Lithuanian Zoological Gardens; Centre: Wikipedia Nilflughund IUCN Red List of Threatened Species; right: Wikipedia Marburg virus CDC Fred Murphy; J. Nakano).

bats contained Marburg virus RNA by RT-PCR; in 2008, Marburg virus carriage was still at 4.5% as expected for a viral reservoir species. All infected bats appeared clinically healthy. Juveniles showed a two-fold higher virus carriage than adults, but transmission was mostly horizontal in the cave. Viral antigen was found in the liver and spleen of two bats from which an infectious virus could be isolated. Two miners infected with Marburg haemorrhagic fever yielded viruses that differed by 21% in the viral genome sequence between the two patients. Different viruses from bats of this cave shared >99% sequence identity with each of the viruses from the two miners (Towner et al. 2007).

Similar data were reported for *R. aegytiacus* bats from a cave in South Africa. Blood samples were collected from 1400 animals: 53% were positive for serum antibodies to Marburg virus. Seropositivity increased from 15% in April to 82% in October 2013. The increase was particularly high in juveniles (1%–77%). Seroconversions were observed in 19% of recaptured bats. Two percent of liver–spleen samples were positive for Marburg virus RNA (Pawęska et al. 2018). *R. aegytiacus* was also a likely Marburg virus reservoir in Zambia: 44% of the bats showed serum antibodies to the Marburg virus. The seroprevalence showed seasonal variation that coincided with the reproductive cycle of these fruit bats (Changula et al. 2018). In another study, researchers found that tissue homogenates from 2 out of 71 cave-dwelling *R. aegytiacus* bats were positive for Marburg virus RNA (Kajihara et al. 2019).

4 | Bat Virus Links With Rabies Infections

Bites of dogs infected with lyssavirus cause rabies in humans. Without postexposure prophylaxis, rabies in humans is inevitably fatal. The lyssavirus genus within the Rhabdoviridae family contains 18 viral species, subdivided into three phylogroups. Bats are the natural hosts of 16 lyssavirus species. Surveys from Taiwan showed that nearly 1% of bat carcasses yielded lyssaviruses (Hu et al. 2018, 2022). Similarly, 15 of 1230 bat brain samples from Germany yielded EBLV-1 (European bat lyssavirus 1) positive samples; all were from serotine bats (*Eptesicus serotinus*) (Figure 4), a Microchiroptera (modern taxonomy suborder: Yangochiroptera, family: *Vespertilionidae*) (Klein et al. 2021). All bat lyssaviruses can infect other mammals including humans and cause fatal rabies. In fact, over a decade, 27 human rabies cases have occurred in the United States; 20 of them have been attributed to bat-associated lyssavirus species, 15 of them belonged to the same eastern pipistrelle bat virus variant (CDC 1999). Pipistrelle is another Yangochiroptera microbat. In the United States and Canada; 41 human bat rabies virus variant cases were observed until 2015. All cases were fatal. Patients reported bites from a bat or unprotected physical contact with bats (Dato et al. 2016). The incidence of bat rabies cases increased in the United States by threefold over the last decades (De Serres et al. 2008). Rare cases of bat lyssaviruses have also been documented in Europe with EBLV-1 (Regnault et al. 2022) and EBLV-2 (Fooks et al. 2003).

EBLV-1–neutralising antibodies were detected in 6% of 700 insectivorous bats collected in North Africa (Serra-Cobo et al. 2018). A study from Spain investigating 2400 bat sera observed neutralising antibodies against EBLV-1 bat lyssavirus in 21% of animals (27% in dead bats). Seroprevalence varied between 3% and 37% according to region and reached up to 40% in *Vespertilionidae* bats. Seroprevalence showed seasonal variation with summer peaks and increased with colony size and the number of bat species living together (Serra-Cobo et al. 2013).

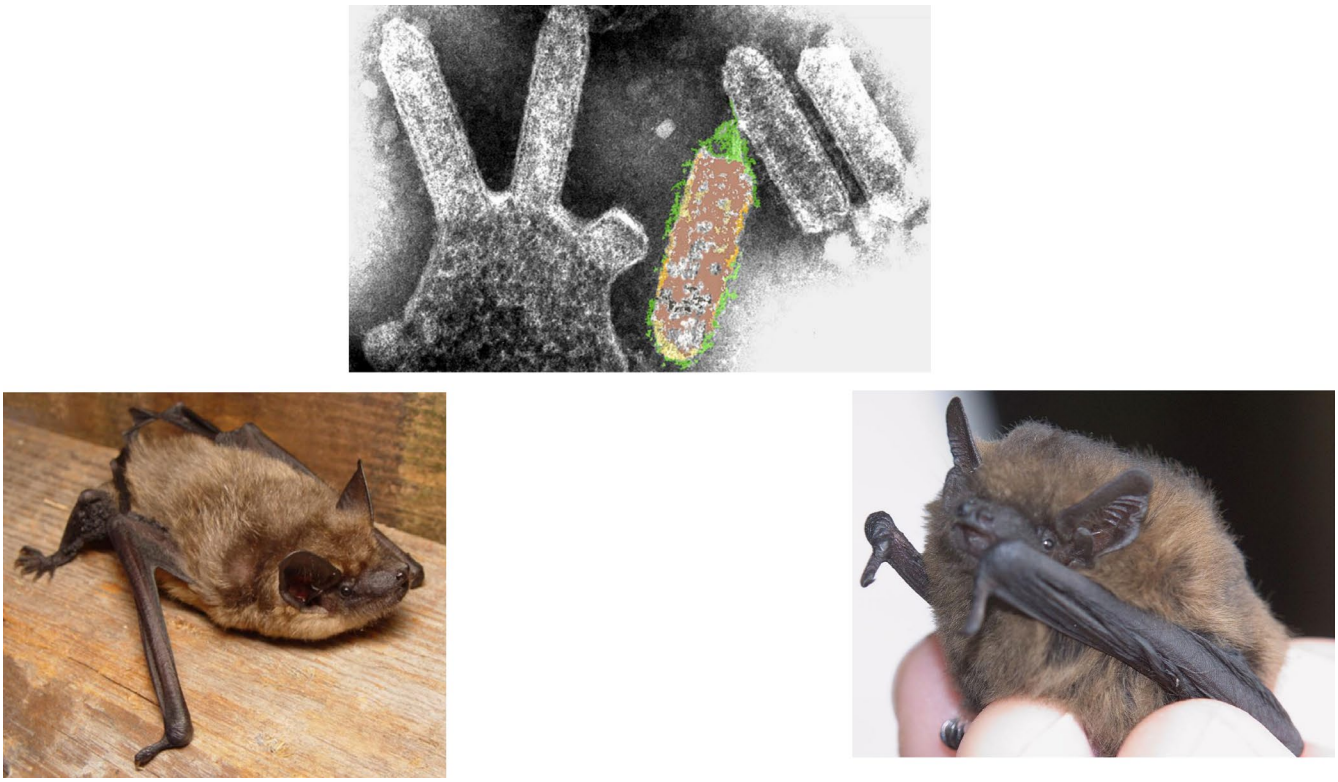

FIGURE 4 | Bat and lyssavirus. Left: Serotine bat *Eptesicus serotinus*, carrier of Lyssavirus; Centre: Electron microscopy of a bat lyssavirus, at the left side budding from an infected cell; Right: A pipistrelle bat, another carrier of lyssavirus (figure credits: left: Wikipedia serotine bat Mnolf; centre: Wikipedia lyssavirus CSIRO; right: Wikipedia common pipistrelle Drahkrub).

Conflicting data exist on whether lyssavirus infections cause pathology in bats. Field studies suggest mild or asymptomatic lyssavirus infections in bats. In two longitudinal studies from France, survival and recapture probabilities were not affected by the serological status of individuals, indicating that bats were exposed to lyssavirus without dying from the infection (Robardet et al. 2017). A Spanish study reported EBLV-1 antibodies in 10% of 550 healthy bats. Antibody-positive bats were recaptured in a healthy condition in the following campaigns. Similar body conditions were observed in bats with oropharyngeal swabs that were positive or negative for lyssavirus RNA (Vázquez-Morón et al. 2008). In contrast, experimental infections in bats with lyssavirus induced disease. Serotine bats experimentally inoculated with EBLV-1 by the intracerebral and subcutaneous route died from rabies, while upon intramuscular and intranasal inoculation, few or no bats died from rabies (Freuling et al. 2009).

5 | Bats Are Reservoir Species for Viral Pathogens: Reoviruses and Further Paramyxoviruses

5.1 | Reovirus

A man from Melaka, Malaysia, developed a respiratory disease with high fever. One week later, two of his children developed a similar disease. A virus was isolated from the index case which turned out to be an Orthoreovirus (double-stranded RNA virus of the *Reoviridae* family). It was genetically and serologically closely related to Pulau virus from fruit bats. One week before the disease onset, a bat intruded the living room of the family. Thirteen percent of 109 human sera from Malaysia neutralised both the Melaka and Pulau viruses (Chua et al. 2007). A respiratory disease was seen in another patient from Malaysia who transmitted the infection to his doctor. The index case yielded another genetically and serologically related Kampar reovirus. The patient's home was frequently visited by fruit bats (Chua et al. 2008). Another adult from Malaysia developed a high fever and prostrating myalgia. The convalescent serum of the patient neutralised the isolated Sikamat reovirus and cross-neutralised several bat reoviruses. Fruit bats had occasionally intruded his weekend house (Chua et al. 2011). More than 60% of *P. hypomelanus* bats showed serum antibodies against bat-like reoviruses isolated from human cases. Human exposure to bat reoviruses seems to be widespread since serum antibodies against bat-like reoviruses were observed in up to 18% of the Malaysian population (Leong et al. 2022).

5.2 | Further Paramyxoviruses

Bats are also healthy carriers of numerous paramyxoviruses beyond NiV and HeV. A study from Madagascar screened 140 bats belonging to four bat families with a pan-paramyxovirus RT-PCR. A positive signal was seen in 41 bats (Wilkinson et al. 2014). In a follow-up eco-epidemiological study with 950 bats, 10% of the bats were infected. Gene sequencing demonstrated that all viruses belonged to unclassified morbilli-related paramyxoviruses. These viruses showed little host specificity, and sympatric occurrence of bats was identified as a major factor for virus transmission

(Mélade et al. 2016). Also, 21% of infected but healthy vampire bats from Brazil contained novel paramyxoviruses when kidney tissue was investigated with high-throughput sequencing (de Souza et al. 2021). US researchers screened 358 healthy individuals from 15 rodents and 18 bat species for the presence of paramyxoviruses: 36% of rodents and 9% of bats gave a positive signal. The bat viruses formed a single clade, representing a distant relative of Henipaviruses (Larsen et al. 2022). A much greater diversity of paramyxoviruses was detected when a worldwide sample of nearly 5000 bats representing 86 species was screened by RT-PCR. This study identified a Rubulavirus in bats that shared sequence relatedness with the human mumpsvirus, with which it formed a single serogroup. In addition, they detected novel members of the genus Morbillivirus. Many new species of Henipaviruses were detected in African bats. Close relatedness with NiV was demonstrated by immunofluorescence. The researchers also detected a novel bat Pneumovirus that formed a sister clade to the human and bovine respiratory syncytial virus. Virus-positive bats were investigated for viral tissue distribution. In *E. helvum* bats, the highest viral loads were detected in the spleen for a Henipavirus. A colony of *Myotis* bats shed morbilli-like viruses at constant concentrations over several years. Blood chemistry showed no signs of inflammation or overt clinical disease in infected bats. The identified bat viruses were not identical to those endemic in humans or livestock (Drexler et al. 2012).

While these bat Paramyxoviruses are so far only potential pathogens, one bat-borne Paramyxovirus, Menangle virus, caused a decline of piglets by 27% in an Australian piggery. The farmers observed mummified and stillborn piglets with a severe degeneration of the brain and the spinal cord. Older pigs were not affected. Two workers on the piggery experienced an unexplained, self-resolving febrile disease during the episode. The pigs and the workers showed neutralising antibodies against the viruses isolated from the lungs, brains and hearts of diseased piglets. These antibodies were not seen in the piggery before the outbreak. A third of fruit bats of different *Pteropus* species showed antibodies against this virus, but none of the wild or other farm animals, suggesting *Pteropus* bats as viral reservoirs (Philbey et al. 1998).

6 | Bat Viruses at the Root of Important Pathogens: Hepaciviruses and Influenza A Viruses

6.1 | Flaviviruses

An international consortium investigated serum specimens from 415 healthy African and Central American bats by high-throughput sequencing. They detected flavivirus-related sequences in the serum pools. Overall, 0.6% and 4%, respectively, of the sera were positive for Hepacivirus and Pegivirus. When extending the search to 1160 serum samples from bats of Nigeria, Bangladesh and Mexico, 23 gave a positive result. All were from insectivorous bats. The viral load ranged from 10^3 to 10^8 RNA copies/mL. Based on partial gene sequencing, a highly diverse group of viruses was identified that clustered within the Hepacivirus (containing the human Hepatitis C virus) and Pegivirus (containing primate flaviviruses) genera. Phylogenetic analysis suggested bats as an ancient reservoir for Hepaci viruses (Quan et al. 2013).

6.2 | Influenza Viruses

Wild populations of waterfowl are reservoirs of influenza A viruses (IAV). IAV display 16 distinct alleles of the HA gene and nine alleles of the NA gene. Human, swine and equine influenza viruses are thought to have emerged from this avian reservoir. When screening rectal swabs from 316 bats representing 21 different species from Guatemala, researchers detected three positive individuals with a pan influenza RT-PCR assay. All three belonged to a single frugivorous bat species, indicating that 10% of this species carried IAV. Up to 10^6 viral genome copies per 100 μL of rectal swab were observed. Liver, intestine, lung and kidney tissues were virus-positive, suggesting active viral replication. Both the viral hemagglutinin HA gene and the viral neuraminidase NA gene differed substantially from known HA and NA genes, defining a new H17N10 influenza virus (Tong et al. 2012). These researchers then screened 110 bats from Peru, representing 18 species: one fruit bat tested positive. Sequencing defined a new H18N11 IAV. Phylogenetic analysis showed that seven of the eight genes of both the Guatemalan and the Peruvian bat IAV were closely related and ancestral to all known IAV. Half of the sera from the investigated 110 Peruvian bats showed specific IgG to the bat HA and NA; 10% showed very high antibody titres suggesting circulation of these viruses in the bat population (Tong et al. 2013).

7 | Why Are Bats Common Suspects for Viral Transmission?

7.1 | Genomic Evidence

Scientists have searched the genomes of bats for hints as to why they can handle viral infections (perhaps with the exception of lyssavirus) without developing obvious clinical symptoms that are lethal for other mammalian families. Two hypotheses were initially considered: either bats mount a more efficient antiviral response that better controls viral replication or bats evolved a tolerance towards viruses which suppresses the pathological sequels of viral infections without inhibiting viral replication. US researchers addressed this question by searching a 1.9 Gb draft genome of *Rousettus aegyptiacus*, known as an asymptomatic carrier of the highly lethal Marburg virus, for immunity-related genes (Pavlovich et al. 2018). When comparing with other mammalian genomes, they observed in the bat genome a significant expansion of several gene families. Key immunity genes showed signs of positive selection. Most notable was an expansion of type I interferon genes. The greatest expansion occurred in the IFN-ω subfamily, which has 55 copies in Rousette bats but only one copy in humans. An antiviral function was demonstrated in cell culture for IFN-ω4 against vesicular stomatitis test virus. Six of ten natural killer receptor genes encode both activating and inhibitory interaction domains. Inhibitory signalling dominated in uninfected bats. MHC class I genes were also found to expand outside of the canonical MHC locus. Based on this first analysis, the researchers concluded that the bat immune system is associated with enhanced infection tolerance rather than enhanced viral defence.

There are about 1400 bat species. It is thus risky to generalise observations from the genome of a single bat species. Therefore an international consortium sequenced the genomes from six bat species (*Rhinolophus ferrumequinum, Rousettus aegyptiacus, Phyllostomus discolor, Myotis, Pipistrellus kuhlii* and *Molossus molossus*) representing the two suborders of Yinpterochiroptera and Yangochiroptera (Jebb et al. 2020). Genomic data were complemented by transcriptome data. The bat genome sizes were, with 2 Gb, significantly smaller than that of other placental mammals, which are typically 2.5–3 Gb large. On this data set, the scientists conducted searches for gene selection, as well as gene losses and gains. Evidence for strong positive selection was identified for genes involved in hearing, laryngeal echolocation and for several immunity-related genes. Selected immunity genes included a B-cell chemokine, interleukins involved in immune system regulation and NF-κB activation and genes involved in responses to pathogens. Gene losses comprised pro-inflammatory interleukins that induce the canonical NF-κB pathway and other pro-inflammatory cytokines. Within gene gains, an expansion of the APOBEC gene family was most notable; these genes encode DNA- and RNA-editing enzymes that are implicated in restricting viral infection and transposon activity. Interestingly, the smaller genome size of bats was related to a lower transposable element content. The authors concluded that bats had evolved immunomodulatory mechanisms that enabled a higher tolerance to pathogens than is typical among mammals.

In a recent publication this research consortium extended the approach by sequencing 10 further bat genomes which included sequenced rhinolophid and hipposiderid bat species, mostly from Southeast Asia, a hotspot for zoonotic disease with bat viruses. The tenth sequenced bat genome was from *Mops condylurus* (family: Molossidae), a natural reservoir of *Orthoebolavirus*. When compared with 95 non-bat mammalian genomes, the most significant enrichment in bat genomes was for immunity-related genes (Morales et al. 2025). This group of genes specifically included 'immune response', 'regulation of immune system process', 'immune effector process' and 'leukocyte activation' genes. The genes selected in bats referred to viral entry and detection factors, and regulators of antiviral and inflammatory responses. The selection had occurred in basal branches of bats and the researchers tentatively connected these immune-related changes to the evolution of flight in bats. The researchers focused on *ISG15*, which is an antiviral gene contributing to hyperinflammation during COVID-19 disease. ISG15 is an ubiquitin-like protein that is strongly induced by IFN-I during viral infections and upregulated in patients with COVID-19. Free ISG15 can be conjugated to hundreds of newly synthesised host and viral proteins (termed ISGylation), helping to restrict virus replication. A highly conserved Cys residue of ISG15 is deleted in bats which prevents its dimerisation. ISG15 from bats showed antiviral activity against influenza A virus and 80% reduced SARS-CoV-2 production in cultured cells, which was not seen with the human ISG15 homologue.

Chinese researchers sequenced the genome of the fruit bat *Cynopterus sphinx* and compared it with that of other bat genomes (Tian et al. 2023). Fruit bats (*Pteropodidae*), which have been observed to be reservoirs for several viruses, had higher evolution/mutation rates in immunity-related genes than other bats. The changes included the loss of the inflammasome-associated NLRP1 gene, a duplication of the C5AR2 gene encoding a receptor of the complement anaphylatoxin C5a, which regulates NLRP3 inflammasome activation, and pteropodid-specific mutations in MyD88, which decreased the levels of inflammatory cytokines (i.e., IL8, IL6 and TNFα) in transformed human cells stimulated by the E protein of SARS-CoV-2.

7.2 | Dampened Inflammation in Bats

NLRP3 is an important sensor that recognises cellular stresses, mitochondrial damage and viral or bacterial infections. NLR stands for nucleotide-binding domain leucine-rich repeat. NLRP3 is a component of the innate immune system that is activated by the pattern recognition receptor (PRR) that recognises pathogen-associated molecular patterns (PAMP) (Figure 5). Following priming and activation signals, NLRP3 triggers the assembly of the ASC protein to form cytologically visible ASC specks. ASC stands for apoptosis-associated speck-like protein containing CARD, where CARD stands for caspase recruitment domain. Hence, ASC recruits and activates caspase-1, which then promotes inflammatory cell death via pyroptosis with cleavage and secretion of the potent pro-inflammatory cytokine interleukin-1β (IL-1β). Researchers from China and Singapore demonstrated that bats showed exon skipping in NLRP3, which deletes a leucine-rich repeat (LRR) domain of NLRP3 (Ahn et al. 2019). ASC speck formation and IL-1β cleavage/secretion by bat NLRP3 isoforms were lower than that mediated by human NLRP3. They subsequently showed that NLRP3-mediated inflammation is dampened in bat immune cells in response to three different types of RNA viruses. These experiments included H1N1 influenza A virus, a bat-borne zoonotic reovirus and MERS coronavirus. These viruses represent three different viral replication strategies, namely a negative single-strand, a double-strand and a positive single-strand RNA virus, respectively, following distinct viral replication strategies. Notably, the dampened inflammation response was mediated by bat NLRP3 in cell culture without a parallel decrease in viral titre. The researchers concluded that their observations support an enhanced innate immune tolerance rather than an enhanced antiviral defence in bats.

In a follow-up study, Ahn et al. (2023) described ASC2 in bats, which miss, like their human ACS2 homologue, the CARD domain and should therefore be unable to activate caspase. Human ASC2 is poorly expressed and undetectable in most human tissues. In contrast, ASC2 is constitutively expressed at a high level in bat immune cells. In addition, bat ASC2 was significantly more potent than human ASC2 in inhibiting human NLRP3 and AIM2 inflammasomes. AIMS is a receptor recognising double-stranded DNA in the cytoplasm, which also activates ACS and an inflammatory response parallel to the action of NLRP3 activated by PRR. Transgenic expression of bat ASC2 in mice reduced the severity of peritonitis induced by gout crystals. Wildtype mice suffered 100% mortality after infection with influenza A virus, while bat ACS2 transgenic mice showed only 50% mortality, and lung IL-1β levels were halved compared to wildtype mice. In contrast, lung influenza viral titres did not differ between both groups of mice. Reduction of IL-1β secretion

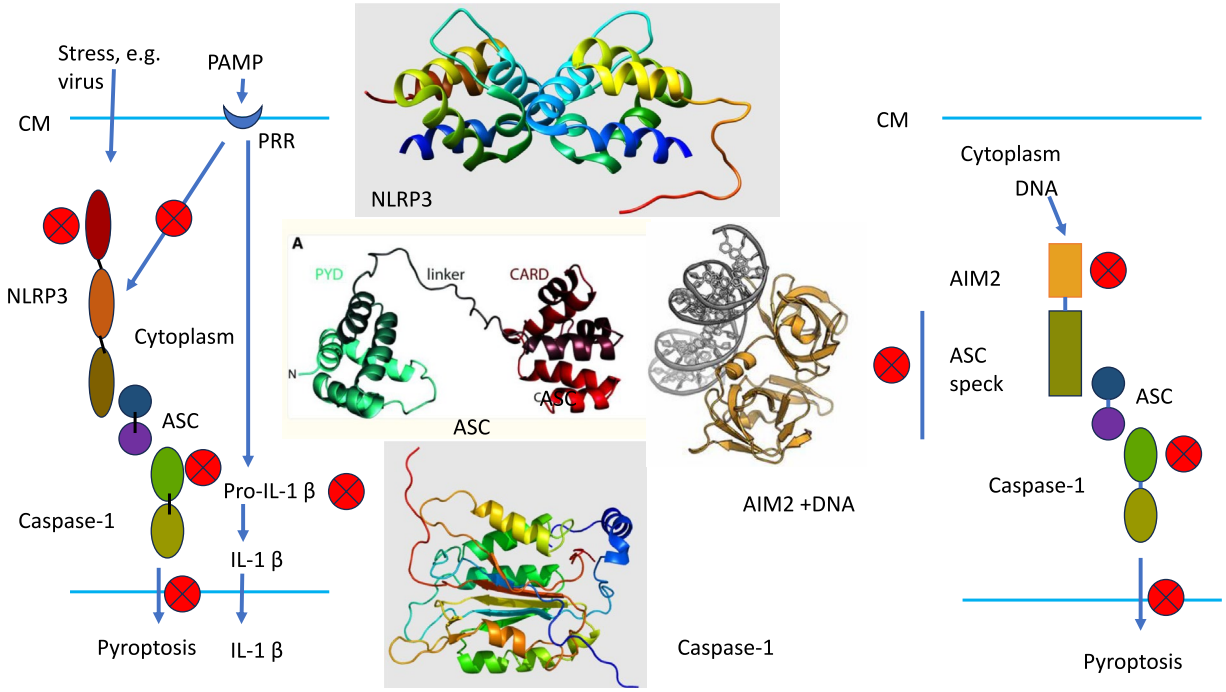

FIGURE 5 | Dampened inflammasome activation in bats. Left: The signalling pathway in human or mouse cells responding to stress signals including viral infection via NLRP3 → ASC → Caspase-1 activation resulting in pyroptosis and in parallel the pattern recognition receptor (PRR) responding to pathogen-associated molecular pattern (PAMP) resulting in pro-IL-1 β cleavage, release of IL-1 β and interacting with NLRP3. For further details see text. Right: Signalling of double-stranded DNA detection in the cytoplasm via the AIM2 inflammasome with intact ASC speck formation, resulting in pyroptosis. The protein domains that are deleted or mutated in bats and interactions that are inhibited in bat cells are marked by a cross in a red circle symbol. Centre: Top: Crystal structure of NLRP3 (PDB 3QF2). Middle, left: NMR structure of ASC (PDB ID: 2KN6) showing the PYD, the flexible linker and the CARD domain. Middle, right: Crystal structure of $AIM2^{HIN}$ bound to dsDNA (PDB ID: 3RN5). AIMS consist of two domains PYD and HIN. Bottom: Structure of caspase-1. Figure credit: The figure was adapted from information from Ahn et al. (2019); Bergsbaken et al. (2009); Hoss et al. (2017); Irving et al. (2021) and Wang and Yin (2017). Structures are from Wikipedia NLRP3 and Wikipedia Caspase-1; PDB 3QF2, PDB ID: 2KN6, PDB ID: 3RN5 and PDB 1bmq.

was also seen in immune cells from transgenic mice infected with Zika virus and a bat reovirus. Bat ACS2 also suppressed SARS-CoV-2 immune-complex-induced inflammasome activation. The researchers defined four amino acid changes in the bat ACS2 responsible for the gain of function compared to the human ACS2. Therefore, modifications of both NLRP3 and ACS2 dampen inflammasome activity in bats.

8 | A Bit of Bat Zoology

One might ask why bats evolved a special relationship with viruses permitting viral replication (making bats a reservoir for many pathogens) without (in most cases) causing an overt disease in bats by viruses that can be lethal to other mammalians, including humans. To address this peculiar question, the title of a 1973 essay by Theodosius Dobzhansky comes to mind 'Nothing in Biology Makes Sense Except in the Light of Evolution'. One should therefore seek possible answers to this conundrum in the evolution of bats. It must be stressed that the following reflections while based on zoological knowledge (Eisentraut 1972; Starck 1995) must remain speculative and are at best plausible hypotheses from evolutionary hindsight.

Bats are peculiar among mammals. They are the only mammalian order to have evolved powered flight. This has caused physiological challenges (e.g., concerning cellular mechanisms to handle the increased oxygen consumption in flight muscles). At the same time, it opened enormous evolutionary possibilities for living in the air, which were not exploited by the rest of mammals that are restricted to terrestrial and aquatic habitats. Birds and insects have also conquered the air; the first could be competitors, if not predators, of bats, while the second represents an abundant food source for bats. To avoid bird competition, bats have maintained the nocturnal lifestyle of their probable insectivore mammalian ancestors, while most birds are day-active. Owls are one of the few nocturnal birds of prey, but their role as predators of bats is limited. From checking stomach contents in owls, only 0.1% of the content is represented by captured bats. Birds have just evolved one species that specialises in bat prey (*Machaerhamphus alcinus*). In addition, some snakes attack bats in their daytime rest locations. However, loss by these predators is very limited for bats.

Selection forces have re-modelled the body of bats in dramatic ways when considering the anatomical changes that the upper extremities and the shoulder girdle experienced in the adaptation to flight. The remodelling of the head appendages for sending and receiving ultrasound in echolocation is another fascinating chapter of 'creative' bat evolution. Bats have also evolved interesting strategies of thermoregulation. During species radiation, bats have learned to exploit a wide range of food

sources from fruits, nectar, pollen and fleshy flowers to small vertebrates including fishes, blood-licking on large mammals and foraging on insects. This food versatility, lack of predation and mobility by flight combined with an unusual longevity of bats assured a worldwide distribution of bats. With the exception of deserts and polar areas, bats are found in virtually all regions of the world. This remarkable geographical and ecological dispersion of bats translated into a split of 1400 currently known bat species. With that number, bats represent 20% of the species of mammals, second only to the Rodentia order. This ecological success also translated in a large number of individuals in bat populations. Mass congregations of bats are observed at daytime rest positions of bats in and on trees and in caves. Researchers have, for example, counted nine million *Tadarida brasiliensis* bats living in a single cave in New Mexico. Rousettus bats displayed a density of 450 individuals per square metre. Bats are furthermore very social, creating, for example, nurseries for the young which are cared for by females that are not necessarily their mothers, allowing social mixing.

9 | Opportunities for Bat Parasites

This zoological success story could also have dark sides. Concentrating large populations of social animals into confined spaces (trees, tree holes, caves) (Figure 6) for daytime rest or hibernation could make them ideal targets for parasites. This has indeed occurred: a classic example is the flightless fly, *Nycteribia vexata*, a blood-sucking insect that exclusively lives on bats. Fleas, lice and mites are common parasites in bat colonies. A recent addition is the fungus *Pseudogymnoascus destructans* that causes White-Nose syndrome in hibernating bats of North America, which has since 2018 dramatically reduced bat populations in the United States (Isidoro-Ayza and Klein 2024). Bat colonies, particularly in caves, provide thus exquisite propagation possibilities for parasites. It would be surprising if viruses would not have 'exploited' this conducive ecological niche presented by gregarious bats. Large populations confined to tree holes or caves are ideal places for virus transmission. Further factors could favour the spread of viral epidemics among bats: caves are frequently inhabited by more than one bat species which are not necessarily physically segregated in the caves. Powered by flight, bats spread out for foraging, where fruit bats from different roosts meet in large numbers on fruit trees. One should therefore anticipate that viral epidemics threatened the survival of dense bat populations unless bats had evolved ways to co-exist with their viruses. In view of the evolutionary malleability of the bat body, it would be surprising if this evolutionary flexibility would not extend to the cellular and molecular levels.

Some scientists have noted a similarity in the lifestyle of bats and humans: both are very numerous, they live in confined places, are very social, globally distributed and highly mobile by flight. The current pace of viral epidemics in the human population demonstrates that viruses 'know' to exploit these favourable transmission possibilities. One might ask why human societies that share characteristics with bat populations have not developed the same tolerance to viruses as bats. The difference is in time: bats were exposed to challenges with RNA viruses for millions of years. At Messel/Germany, 50-million-years-old fossils of bats were found that resemble extant bat skeletons. Bats had thus long time periods to adapt to challenges, while humans experienced living under crowded conditions for only a few thousand years, too short a time period to adapt through biological evolution. Humans definitively need science and technology to learn lessons from bats on how to deal with viral infections and to come to grip with viral pandemics.

FIGURE 6 | High-density bat populations favour virus transmission. Left: Daytime resting place of *Pteropus* bats in a roost tree, Right, top: Bats leaving a cavern (motion video in Wikipedia under 'Bracken cave' entry); Right, bottom: Common Vampire Bat, *Desmodus rotundus*, colony in a tree hole (figure credits: Left: Wikipedia Pteropus Vladimir Yu. Arkhipov, Arkhivov, right top: Wikimedia Commons Theora/Vorbis; right bottom: Wikipedia bat, Uwe Schmidt).

There are advantages in suppressing the pathological consequences of viral infections without curtailing viral replication. One is theoretical: Viruses are 'interested' to replicate their genome while viral pathology is not a primary goal of viruses. Thus evolutionary theory would predict that modifying pathological sequels without suppressing viral replication is easier to achieve than to eliminate viruses in the first place. Indeed, current research revealed that viruses developed sophisticated means to counteract the resistance mechanisms of the host preventing viral replication. There is another aspect that makes the bat viral tolerance and not viral elimination strategy attractive. Case reports suggested that humans acquired viral infections when intruding into caves inhabited by bats. This has been reported for Marburg virus infections (see above) and also for rare cases of rabies infections of persons exposed to caves inhabited by *Tadarida brasiliensis* bats in Texas (Manning et al. 2008). Virus concentrations in bat caves (air by exhalation, ground by faeces and urine) are not well documented (for an overview: Willoughby et al. 2017) but the infection risk for human explorers (or eco-tourists) might be substantial, as suggested by the protective gear used by virologists exploring bat caves for coronaviruses and the regulatory request to conduct the screening of bats for viruses under the highest biosecurity level or to stop these activities altogether.

If bats allow viruses to replicate on them, bats could use these viruses to defend their habitat against intruders. As humans are now global intruders in the ecosphere, we might increasingly be confronted with viruses that bats learned to handle ('domesticate'?) and could use to deter or kill intruders. The use of viruses for defending an ecological niche is not a new concept: bacteria have long ago discovered such strategies. Lysogenic bacterial cells containing prophages frequently release induced prophages that can kill competitor cells. Competitors are susceptible to the released bacterial virus while the producer clone resists infection due to immunity genes of the prophage. Many bacteria use, in addition, bacteriocins to kill ecological competitors. Some bacteriocins still show that they were derived from bacteriophages that were remodelled by the bacteria as molecular weapons for biological warfare. One might therefore wonder whether bats 'invented' viral tolerance as a strategy to use the released viruses as biological weapons against intruders into their habitat. The combination of viral tolerance and biological 'weaponisation' of the released viruses might explain why we see so many bat-associated emerging viral infections in animals and humans.

Bats are evolutionary specialists, having evolved many adaptive traits including viral tolerance, which have contributed to their ecological success. However, general evolutionary theory assumes that viruses which live long enough with their host evolve for efficient replication while attenuating viral pathogenicity for the host. Only when a spillover to a new host occurs, the lack of adaptation in the new virus–host system could cause major pathology. Models of climate change and environmental deterioration predict that many mammalian species will adapt their geographical range and migrate to seek habitable niches (Carlson et al. 2022). As a consequence, many new encounters between animals will occur that have never met in the past, including new animal–human contacts. If the concept of using viruses as ecological weapons to which a given host has developed tolerance is correct, we might expect many emerging viral diseases in the near future.

Author Contributions

Harald Brüssow: conceptualization, investigation, writing – original draft, writing – review and editing.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

Ahn, M., D. E. Anderson, Q. Zhang, et al. 2019. "Dampened NLRP3-Mediated Inflammation in Bats and Implications for a Special Viral Reservoir Host." *Nature Microbiology* 4, no. 5: 789–799. https://doi.org/10.1038/s41564-019-0371-3.

Ahn, M., V. C. Chen, P. Rozario, et al. 2023. "Bat ASC2 Suppresses Inflammasomes and Ameliorates Inflammatory Diseases." *Cell* 186, no. 10: 2144–2159.e22. https://doi.org/10.1016/j.cell.2023.03.036.

Anderson, D. E., A. Islam, G. Crameri, et al. 2019. "Isolation and Full-Genome Characterization of Nipah Viruses From Bats, Bangladesh." *Emerging Infectious Diseases* 25, no. 1: 166–170. https://doi.org/10.3201/eid2501.180267.

Becker, D. J., P. Eby, W. Madden, A. J. Peel, and R. K. Plowright. 2023. "Ecological Conditions Predict the Intensity of Hendra Virus Excretion Over Space and Time From Bat Reservoir Hosts." *Ecology Letters* 26, no. 1: 23–36. https://doi.org/10.1111/ele.14007.

Bergsbaken, T., S. L. Fink, and B. T. Cookson. 2009. "Pyroptosis: Host Cell Death and Inflammation." *Nature Reviews. Microbiology* 7, no. 2: 99–109. https://doi.org/10.1038/nrmicro2070.

Carlson, C. J., G. F. Albery, C. Merow, et al. 2022. "Climate Change Increases Cross-Species Viral Transmission Risk." *Nature* 607, no. 7919: 555–562. https://doi.org/10.1038/s41586-022-04788-w.

CDC. 1999. "Case Reports: Human Rabies–Virginia, 1998." *MMWR. Morbidity and Mortality Weekly Report* 48, no. 5: 95–97.

Changula, K., M. Kajihara, A. Mori-Kajihara, et al. 2018. "Seroprevalence of Filovirus Infection of *Rousettus aegyptiacus* Bats in Zambia." *Journal of Infectious Diseases* 218, no. suppl_5: S312–S317. https://doi.org/10.1093/infdis/jiy266.

Chua, K. B., W. J. Bellini, P. A. Rota, et al. 2000. "Nipah Virus: A Recently Emergent Deadly Paramyxovirus." *Science* 288, no. 5470: 1432–1435. https://doi.org/10.1126/science.288.5470.1432.

Chua, K. B., B. H. Chua, and C. W. Wang. 2002. "Anthropogenic Deforestation, El Niño and the Emergence of Nipah Virus in Malaysia." *Malaysian Journal of Pathology* 24, no. 1: 15–21.

Chua, K. B., G. Crameri, A. Hyatt, et al. 2007. "A Previously Unknown Reovirus of Bat Origin Is Associated With an Acute Respiratory Disease in Humans." *Proceedings of the National Academy of Sciences of the United States of America* 104, no. 27: 11424–11429. https://doi.org/10.1073/pnas.0701372104.

Chua, K. B., K. J. Goh, K. T. Wong, et al. 1999. "Fatal Encephalitis due to Nipah Virus Among Pig-Farmers in Malaysia." *Lancet* 354, no. 9186: 1257–1259. https://doi.org/10.1016/S0140-6736(99)04299-3.

Chua, K. B., C. L. Koh, P. S. Hooi, et al. 2002. "Isolation of Nipah Virus From Malaysian Island Flying-Foxes." *Microbes and Infection* 4, no. 2: 145–151. https://doi.org/10.1016/s1286-4579(01)01522-2.

Chua, K. B., K. Voon, G. Crameri, et al. 2008. "Identification and Characterization of a New Orthoreovirus From Patients With Acute Respiratory Infections." *PLoS One* 3, no. 11: e3803. https://doi.org/10.1371/journal.pone.0003803.

Chua, K. B., K. Voon, M. Yu, C. Keniscope, K. Abdul Rasid, and L. F. Wang. 2011. "Investigation of a Potential Zoonotic Transmission of Orthoreovirus Associated With Acute Influenza-Like Illness in an Adult Patient." *PLoS One* 6, no. 10: e25434. https://doi.org/10.1371/journal.pone.0025434.

Daszak, P., C. Zambrana-Torrelio, T. L. Bogich, et al. 2013. "Interdisciplinary Approaches to Understanding Disease Emergence: The Past, Present, and Future Drivers of Nipah Virus Emergence." *Proceedings of the National Academy of Sciences of the United States of America* 110, no. Suppl 1: 3681–3688. https://doi.org/10.1073/pnas.1201243109.

Dato, V. M., E. R. Campagnolo, J. Long, and C. E. Rupprecht. 2016. "A Systematic Review of Human Bat Rabies Virus Variant Cases: Evaluating Unprotected Physical Contact With Claws and Teeth in Support of Accurate Risk Assessments." *PLoS One* 11, no. 7: e0159443. https://doi.org/10.1371/journal.pone.0159443.

De Serres, G., F. Dallaire, M. Côte, and D. M. Skowronski. 2008. "Bat Rabies in the United States and Canada From 1950 Through 2007: Human Cases With and Without Bat Contact." *Clinical Infectious Diseases* 46, no. 9: 1329–1337. https://doi.org/10.1086/586745.

de Souza, W. M., M. J. Fumagalli, J. P. Carrera, et al. 2021. "Paramyxoviruses From Neotropical Bats Suggest a Novel Genus and Nephrotropism." *Infection, Genetics and Evolution* 95: 105041. https://doi.org/10.1016/j.meegid.2021.105041.

Drexler, J. F., V. M. Corman, M. A. Müller, et al. 2012. "Bats Host Major Mammalian Paramyxoviruses." *Nature Communications* 3: 796. https://doi.org/10.1038/ncomms1796.

Eby, P., A. J. Peel, A. Hoegh, et al. 2023. "Pathogen Spillover Driven by Rapid Changes in Bat Ecology." *Nature* 613, no. 7943: 340–344. https://doi.org/10.1038/s41586-022-05506-2.

Eisentraut, M. 1972. *Grzimeks Tierleben. Chapters: Fledertiere, Flederhunde, Fledermäuse*. Vol. 11, 89–161. Kindler Verlag Zürich.

Epstein, J. H., S. J. Anthony, A. Islam, et al. 2020. "Nipah Virus Dynamics in Bats and Implications for Spillover to Humans." *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 46: 29190–29201. https://doi.org/10.1073/pnas.2000429117.

Fooks, A. R., L. M. McElhinney, D. J. Pounder, et al. 2003. "Case Report: Isolation of a European Bat Lyssavirus Type 2a From a Fatal Human Case of Rabies Encephalitis." *Journal of Medical Virology* 71, no. 2: 281–289. https://doi.org/10.1002/jmv.10481.

Freuling, C., A. Vos, N. Johnson, et al. 2009. "Experimental Infection of Serotine Bats (*Eptesicus serotinus*) With European Bat Lyssavirus Type 1a." *Journal of General Virology* 90, no. Pt 10: 2493–2502. https://doi.org/10.1099/vir.0.011510-0.

Gaudino, M., N. Aurine, C. Dumont, et al. 2020. "High Pathogenicity of Nipah Virus From *Pteropus lylei* Fruit Bats, Cambodia." *Emerging Infectious Diseases* 26, no. 1: 104–113. https://doi.org/10.3201/eid2601.191284.

Ge, X. Y., J. L. Li, X. L. Yang, et al. 2013. "Isolation and Characterization of a Bat SARS-Like Coronavirus That Uses the ACE2 Receptor." *Nature* 503, no. 7477: 535–538. https://doi.org/10.1038/nature12711.

Hasebe, F., N. T. Thuy, S. Inoue, et al. 2012. "Serologic Evidence of Nipah Virus Infection in Bats, Vietnam." *Emerging Infectious Diseases* 18, no. 3: 536–537. https://doi.org/10.3201/eid1803.111121.

Hayman, D. T., M. Yu, G. Crameri, et al. 2012. "Ebola Virus Antibodies in Fruit Bats, Ghana, West Africa." *Emerging Infectious Diseases* 18, no. 7: 1207–1209. https://doi.org/10.3201/eid1807.111654.

Hoss, F., J. F. Rodriguez-Alcazar, and E. Latz. 2017. "Assembly and Regulation of ASC Specks." *Cellular and Molecular Life Sciences* 74, no. 7: 1211–1229. https://doi.org/10.1007/s00018-016-2396-6.

Hossain, M. J., E. S. Gurley, J. M. Montgomery, et al. 2008. "Clinical Presentation of Nipah Virus Infection in Bangladesh." *Clinical Infectious Diseases* 46, no. 7: 977–984. https://doi.org/10.1086/529147.

Hu, S. C., C. L. Hsu, F. Lee, et al. 2022. "Novel Bat Lyssaviruses Identified by Nationwide Passive Surveillance in Taiwan, 2018–2021." *Viruses* 14, no. 7: 1562. https://doi.org/10.3390/v14071562.

Hu, S. C., C. L. Hsu, M. S. Lee, et al. 2018. "Lyssavirus in Japanese Pipistrelle, Taiwan." *Emerging Infectious Diseases* 24, no. 4: 782–785.

Irving, A. T., M. Ahn, G. Goh, D. E. Anderson, and L. F. Wang. 2021. "Lessons From the Host Defences of Bats, a Unique Viral Reservoir." *Nature* 589, no. 7842: 363–370. https://doi.org/10.1038/s41586-020-03128-0.

Isidoro-Ayza, M., and B. S. Klein. 2024. "Pathogenic Strategies of *Pseudogymnoascus destructans* During Torpor and Arousal of Hibernating Bats." *Science* 385, no. 6705: 194–200. https://doi.org/10.1126/science.adn5606.

Jebb, D., Z. Huang, M. Pippel, et al. 2020. "Six Reference-Quality Genomes Reveal Evolution of Bat Adaptations." *Nature* 583, no. 7817: 578–584. https://doi.org/10.1038/s41586-020-2486-3.

Kajihara, M., B. M. Hang'ombe, K. Changula, et al. 2019. "Marburgvirus in Egyptian Fruit Bats, Zambia." *Emerging Infectious Diseases* 25, no. 8: 1577–1580. https://doi.org/10.3201/eid2508.190268.

Klein, A., S. Calvelage, K. Schlottau, et al. 2021. "Retrospective Enhanced Bat Lyssavirus Surveillance in Germany Between 2018–2020." *Viruses* 13, no. 8: 1538. https://doi.org/10.3390/v13081538.

Larsen, B. B., S. Gryseels, H. W. Otto, and M. Worobey. 2022. "Evolution and Diversity of Bat and Rodent Paramyxoviruses From North America." *Journal of Virology* 96, no. 3: e0109821. https://doi.org/10.1128/JVI.01098-21.

Leong, W. J., X. F. Quek, H. Y. Tan, et al. 2022. "Seroprevalence of Pteropine Orthoreovirus in Humans Remain Similar After Nearly Two Decades (2001–2002 vs. 2017) in Tioman Island, Malaysia." *Journal of Medical Virology* 94, no. 2: 771–775. https://doi.org/10.1002/jmv.27422.

Leroy, E. M., B. Kumulungui, X. Pourrut, et al. 2005. "Fruit Bats as Reservoirs of Ebola Virus." *Nature* 438, no. 7068: 575–576. https://doi.org/10.1038/438575a.

Li, W., Z. Shi, M. Yu, et al. 2005. "Bats Are Natural Reservoirs of SARS-Like Coronaviruses." *Science* 310, no. 5748: 676–679. https://doi.org/10.1126/science.1118391.

Luby, S. P., M. Rahman, M. J. Hossain, et al. 2006. "Foodborne Transmission of Nipah Virus, Bangladesh." *Emerging Infectious Diseases* 12, no. 12: 1888–1894. https://doi.org/10.3201/eid1212.060732.

Manning, S. E., C. E. Rupprecht, D. Fishbein, et al. 2008. "Human Rabies Prevention–United States, 2008: Recommendations of the Advisory Committee on Immunization Practices." *Morbidity and Mortality Weekly Report. Recommendations and Reports* 57, no. RR-3: 1–28.

Marí Saéz, A., S. Weiss, K. Nowak, et al. 2015. "Investigating the Zoonotic Origin of the West African Ebola Epidemic." *EMBO Molecular Medicine* 7, no. 1: 17–23. https://doi.org/10.15252/emmm.201404792.

McKee, C. D., A. Islam, S. P. Luby, et al. 2021. "The Ecology of Nipah Virus in Bangladesh: A Nexus of Land-Use Change and Opportunistic

Feeding Behavior in Bats." *Viruses* 13, no. 2: 169. https://doi.org/10.3390/v13020169.

Mélade, J., N. Wieseke, B. Ramasindrazana, et al. 2016. "An Eco-Epidemiological Study of Morbilli-Related Paramyxovirus Infection in Madagascar Bats Reveals Host-Switching as the Dominant Macro-Evolutionary Mechanism." *Scientific Reports* 6: 23752. https://doi.org/10.1038/srep23752.

Morales, A. E., Y. Dong, T. Brown, et al. 2025. "Bat Genomes Illuminate Adaptations to Viral Tolerance and Disease Resistance." *Nature* 638, no. 8050: 449–458. https://doi.org/10.1038/s41586-024-08471-0.

Olson, J. G., C. Rupprecht, P. E. Rollin, et al. 2002. "Antibodies to Nipah-Like Virus in Bats (*Pteropus lylei*), Cambodia." *Emerging Infectious Diseases* 8, no. 9: 987–988. https://doi.org/10.3201/eid0809.010515.

Pavlovich, S. S., S. P. Lovett, G. Koroleva, et al. 2018. "The Egyptian Rousette Genome Reveals Unexpected Features of Bat Antiviral Immunity." *Cell* 173, no. 5: 1098–1110.e18. https://doi.org/10.1016/j.cell.2018.03.070.

Pawęska, J. T., P. Jansen van Vuren, A. Kemp, et al. 2018. "Marburg Virus Infection in Egyptian Rousette Bats, South Africa, 2013–2014." *Emerging Infectious Diseases* 24, no. 6: 1134–1137. https://doi.org/10.3201/eid2406.172165.

Pekar, J. E., S. Lytras, M. Ghafari, et al. 2025. "The Recency and Geographical Origins of the Bat Viruses Ancestral to SARS-CoV and SARS-CoV-2." *Cell* 188: 3167–3183.e18. https://doi.org/10.1016/j.cell.2025.03.035.

Pernet, O., B. S. Schneider, S. M. Beaty, et al. 2014. "Evidence for Henipavirus Spillover Into Human Populations in Africa." *Nature Communications* 5: 5342. https://doi.org/10.1038/ncomms6342.

Philbey, A. W., P. D. Kirkland, A. D. Ross, et al. 1998. "An Apparently New Virus (Family Paramyxoviridae) Infectious for Pigs, Humans, and Fruit Bats." *Emerging Infectious Diseases* 4, no. 2: 269–271. https://doi.org/10.3201/eid0402.980214.

Plowright, R. K., P. Foley, H. E. Field, et al. 2011. "Urban Habituation, Ecological Connectivity and Epidemic Dampening: The Emergence of Hendra Virus From Flying Foxes (Pteropus spp.)." *Proceedings of the Royal Society of London, Series B: Biological Sciences* 278, no. 1725: 3703–3712. https://doi.org/10.1098/rspb.2011.0522.

Pourrut, X., A. Délicat, P. E. Rollin, T. G. Ksiazek, J. P. Gonzalez, and E. M. Leroy. 2007. "Spatial and Temporal Patterns of Zaire Ebolavirus Antibody Prevalence in the Possible Reservoir Bat Species." *Journal of Infectious Diseases* 196, no. Suppl 2: S176–S183. https://doi.org/10.1086/520541.

Quan, P. L., C. Firth, J. M. Conte, et al. 2013. "Bats Are a Major Natural Reservoir for Hepaciviruses and Pegiviruses." *Proceedings of the National Academy of Sciences of the United States of America* 110, no. 20: 8194–8199. https://doi.org/10.1073/pnas.1303037110.

Regnault, B., B. Evrard, I. Plu, et al. 2022. "First Case of Lethal Encephalitis in Western Europe due to European Bat Lyssavirus Type 1." *Clinical Infectious Diseases* 74, no. 3: 461–466. https://doi.org/10.1093/cid/ciab443.

Robardet, E., C. Borel, M. Moinet, et al. 2017. "Longitudinal Survey of Two Serotine Bat (*Eptesicus serotinus*) Maternity Colonies Exposed to EBLV-1 (European Bat Lyssavirus Type 1): Assessment of Survival and Serological Status Variations Using Capture-Recapture Models." *PLoS Neglected Tropical Diseases* 11, no. 11: e0006048. https://doi.org/10.1371/journal.pntd.0006048.

Serra-Cobo, J., M. López-Roig, R. Lavenir, et al. 2018. "Active Sero-Survey for European Bat Lyssavirus Type-1 Circulation in North African Insectivorous Bats." *Emerging Microbes & Infections* 7, no. 1: 213. https://doi.org/10.1038/s41426-018-0214-y.

Serra-Cobo, J., M. López-Roig, M. Seguí, et al. 2013. "Ecological Factors Associated With European Bat Lyssavirus Seroprevalence in Spanish Bats." *PLoS One* 8, no. 5: e64467. https://doi.org/10.1371/journal.pone.0064467.

Starck, D. 1995. *Lehrbuch der Speziellen Zoologie. Wirbeltiere: Chiroptera Volume 5, Part 1*, 424–470. Gustav Fischer Verlag.

Temmam, S., K. Vongphayloth, E. Baquero, et al. 2022. "Bat Coronaviruses Related to SARS-CoV-2 and Infectious for Human Cells." *Nature* 604, no. 7905: 330–336. https://doi.org/10.1038/s41586-022-04532-4.

Tian, S., J. Zeng, H. Jiao, et al. 2023. "Comparative Analyses of Bat Genomes Identify Distinct Evolution of Immunity in Old World Fruit Bats." *Science Advances* 9, no. 18: eadd0141. https://doi.org/10.1126/sciadv.add0141.

Tong, S., Y. Li, P. Rivailler, et al. 2012. "A Distinct Lineage of Influenza A Virus From Bats." *Proceedings of the National Academy of Sciences of the United States of America* 109, no. 11: 4269–4274. https://doi.org/10.1073/pnas.1116200109.

Tong, S., X. Zhu, Y. Li, et al. 2013. "New World Bats Harbor Diverse Influenza A Viruses." *PLoS Pathogens* 9, no. 10: e1003657. https://doi.org/10.1371/journal.ppat.1003657.

Towner, J. S., X. Pourrut, C. G. Albariño, et al. 2007. "Marburg Virus Infection Detected in a Common African Bat." *PLoS One* 2, no. 8: e764. https://doi.org/10.1371/journal.pone.0000764.

Vázquez-Morón, S., J. Juste, C. Ibáñez, et al. 2008. "Endemic Circulation of European Bat Lyssavirus Type 1 in Serotine Bats, Spain." *Emerging Infectious Diseases* 14, no. 8: 1263–1266. https://doi.org/10.3201/eid1408.080068.

Wacharapluesadee, S., B. Lumlertdacha, K. Boongird, et al. 2005. "Bat Nipah Virus, Thailand." *Emerging Infectious Diseases* 11, no. 12: 1949–1951. https://doi.org/10.3201/eid1112.050613.

Wang, B., and Q. Yin. 2017. "AIM2 Inflammasome Activation and Regulation: A Structural Perspective." *Journal of Structural Biology* 200, no. 3: 279–282. https://doi.org/10.1016/j.jsb.2017.08.001.

Wilkinson, D. A., J. Mélade, M. Dietrich, et al. 2014. "Highly Diverse Morbillivirus-Related Paramyxoviruses in Wild Fauna of the Southwestern Indian Ocean Islands: Evidence of Exchange Between Introduced and Endemic Small Mammals." *Journal of Virology* 88, no. 15: 8268–8277. https://doi.org/10.1128/JVI.01211-14.

Willoughby, A. R., K. L. Phelps, Predict Consortium, and K. J. Olival. 2017. "A Comparative Analysis of Viral Richness and Viral Sharing in Cave-Roosting Bats." *Diversity* 9: 35. https://doi.org/10.3390/d9030035.

World Health Organization. 2018. "WHO Research and Development Blueprint: 2018 Annual Review of Diseases Prioritized Under the Research and Development Blueprint." (World Health Organization, Geneva, Switzerland).

Yadav, P. D., C. G. Raut, A. M. Shete, et al. 2012. "Detection of Nipah Virus RNA in Fruit Bat (*Pteropus giganteus*) From India." *American Journal of Tropical Medicine and Hygiene* 87, no. 3: 576–578. https://doi.org/10.4269/ajtmh.2012.11-0416.

Yob, J. M., H. Field, A. M. Rashdi, et al. 2001. "Nipah Virus Infection in Bats (Order Chiroptera) in Peninsular Malaysia." *Emerging Infectious Diseases* 7, no. 3: 439–441. https://doi.org/10.3201/eid0703.010312.

Zhou, P., H. Fan, T. Lan, et al. 2018. "Fatal Swine Acute Diarrhoea Syndrome Caused by an HKU2-Related Coronavirus of Bat Origin." *Nature* 556, no. 7700: 255–258. https://doi.org/10.1038/s41586-018-0010-9.

Zhou, P., X. L. Yang, X. G. Wang, et al. 2020. "A Pneumonia Outbreak Associated With a New Coronavirus of Probable Bat Origin." *Nature* 579, no. 7798: 270–273. https://doi.org/10.1038/s41586-020-2012-7.