Bats Prove To Be Rich Reservoirs for Emerging Viruses

Investigators ponder how anatomy, physiology, ecology, and behavior affect how bats host viral pathogens

Charles H. Calisher, Kathryn V. Holmes, Samuel R. Dominguez, Tony Schountz, and Paul Cryan

Emerging pathogens, many of them viruses, continue to surprise us, providing many newly recognized diseases to study and to try to control. Many of these emergent viruses are zoonotic, transmitted from reservoirs in wild or domestic animals to humans, either by insect vectors or by exposure to the droppings or tissues of such animals. One rich—but, until recently, underappreciated—source of emergent viruses is bats (*Chiroptera*, meaning "hand wing"). Accounting for 1,116, or nearly one-fourth, of the 4,600 recognized species of mammals, bats are grouped into two suborders—Megachiroptera, which contains a single family, Pteropodidae, consisting of 42 genera and 186 species, and Microchiroptera, which contains 17 families, 160 genera, and 930 species.

Although bats are among the most abundant, diverse, and geographically dispersed orders of terrestrial mammals, research on these flying mammals historically focused more on their habits and outward characteristics than on their role in carrying microorganisms and transmitting pathogens to other species. Even in those cases where bats were known to carry particular pathogens, the microbiologists who studied those pathogens typically knew little about the bat hosts. Hence, investigators now are seeking to explain how variations of anatomy, physiology, ecology, and behavior influence the roles of bats as hosts for viral pathogens.

Summary

- Bats help to maintain and distribute rabies virus, which some of them harbor asymptomatically.
- Although isolating virus proves it had infected the animal, virus isolation alone does not indicate what role bats play in its natural cycle.
- Several viruses emerged from bats during the past few decades, including Australian bat lyssavirus, Hendra and Nipah henipaviruses, Menangle, severe acute respiratory syndrome (SARS) coronavirus, Lake Victoria marburgvirus, and Zaire ebolavirus.
- Immune evasion mechanisms typically are virus-specific, but little is known about how viruses manipulate bat immune responses.

Bats Are Remarkable

Bats are remarkable animals. They are the only mammals capable of powered flight,

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Viruses isolated from or viral nucleic acid detected in naturally infected bats world-wide, by virus taxon and source[a]

Family	Genus/subfamily	Virus
Rhabdoviridae	*Lyssavirus*	Rabies (numerous, world-wide), Lagos bat, (3), Duvenhage (3), Australian bat lyssavirus (3), European bat lyssavirus 1 (2), European bat lyssavirus 2 (6), Aravan (1), Khujand (1), Irkut (1), West Caucasian bat (1)
	unassigned	Gossas (1), Kern Canyon (1), Mount Elgon bat(1), Oita 296 (1)
Orthomyxoviridae	*Influenzavirus A*	Influenza A virus (1)
Paramyxoviridae	*Henipavirus*	Hendra (4), Nipah virus (3)
	Rubulavirus	Menangle (1), Tioman (1), Mapuera (1)
	undetermined	a parainfluenzavirus (1)
Coronaviridae	*Coronavirus*	(Group 1) coronaviruses (2), (Group 2) SARS coronavirus (4)
Togaviridae	*Alphavirus*	Chikungunya (1), Sindbis (2), Venezuelan equine encephalitis (3)
Flaviviridae	*Flavivirus*	Bukalasa bat (1), Carey Island (2), Central European encephalitis (1), Dakar bat (3), Entebbe bat (2), Japanese encephalitis (3), Jugra (1), Kyasanur Forest disease (2), Montana Myotis leucoencephalitis (1), Phnom-Penh bat (2), Rio Bravo (2), St. Louis encephalitis (1), Saboya (1), Sokuluk (1), Tamana bat (1), Uganda S (1), West Nile (1), Yokose (1)
Bunyaviridae	*Orthobunyavirus*	Catu (1), Guama (1), Nepuyo (2)
	Hantavirus	Hantaan (2)
	Phlebovirus	Rift Valley fever (2), Toscana (1)
	unassigned	Kaeng Khoi (1), Bangui (3)
Reoviridae	*Orbivirus*	Ife (1), Japanaut (1), Fomede (1)
	Orthoreovirus	Nelson Bay (1), Pulau (1), Broome (1), Melaka (1)
Arenaviridae	*Arenavirus*	Tacaribe (2)
Herpesviridae	unassigned	Agua Preta (1), a cytomegalovirus (1), Parixa (1)
	subfamily *Gammaherpesvirinae*	gammaherpesvirus 1 (4), gammaherpesvirus 2 (2), gammaherpesvirus 3 (3), gammaherpesvirus 4 (2), gammaherpesvirus 5 (1), gammaherpesvirus 6 (1), gammaherpesvirus 7 (1)
	subfamily *Betaherpesvirinae*	betaherpesvirus 1 (2)
Picornaviridae	undetermined	Juruaca (1)
Papillomaviridae	new, unnamed	unnamed virus (1)
Adenoviridae	*Mastadenovirus*	Ryukyu virus (1)
Filoviridae	*Marburgvirus*	Lake Victoria marburgvirus (3)
	Ebolavirus	Zaire ebolavirus (3)
Astroviridae	*Mammastrovirus*	Unnamed
Unclassified		Issyk-kul = Keterah (14), Mojui dos Campos (1), Yogue (1), Kasokero (1), Kolenter (1), Ank 6909 (1)

[a]Numbers in parentheses indicate the number of species of bats from which these viruses were isolated or in which their RNA was detected.

and they can fly and navigate in complete darkness. Bats vary tremendously, ranging in size from giant fruit-eating bats, which weigh as much as 1 kg and have 2-m wingspans, to tiny insectivorous forms, which weigh less than 2 gm and have 8-cm wingspans. Bats also exhibit remarkably diverse structures for detecting prey, such as heat sensors in the noses of vampire bats that detect blood sources.

Unlike many other small mammals, bats live as long as 30 years, and reproduce slowly, typically producing only one or two young per year. Bats of many species can reduce their metabolic rates to conserve energy when food or water is limited, and bats of temperate zones hibernate or migrate during the winter. These temperate zone bats typically mate during autumn and winter, and females store viable sperm in their reproductive tracts for weeks to months. The sexes segregate during late spring and summer. Bats regularly form colonies of hundreds to millions, some at densities of 300 individuals per 0.09 m. Despite little evidence that they are susceptible to epizootic diseases, such crowding provides ample opportunity for bat-to-bat transmission of infectious agents.

Bats carry microbial flora that include bacteria, fungi, and parasites. Although bats are susceptible to infections with microbes that infect humans and livestock, whether bats serve as reservoirs from which some of these microbes are transmitted to humans or other species is not known.

Calisher's Interest in Bat-Borne Viruses Is in Addition to His Lifelong Love of Baseball

Long before developing an interest in bat- and rodent-borne viruses, Charles Calisher loved to play baseball. Until a few years ago, the 72-year-old microbiologist officiated baseball games for youth and college leagues, pursuing his interest in this sport that he still deems "fun and challenging." Since retiring from those umpiring duties, however, he continues to work in virology, which he calls "interesting and functional," as a professor of microbiology at the College of Veterinary Medicine and Biomedical Sciences of Colorado State University in Fort Collins.

"Don Zimmer said that he had been a [baseball] player, coach, and manager for more than 60 years and had never worked a day in his life," Calisher says. "I feel the same." However, unlike Zimmer, Calisher "started out as a bacteriologist but switched to studying viruses when I heard that there were such things as antibiotics. Turns out that [view] was shortsighted, but I have never regretted the decision. I am just as fascinated with viruses today as I was 50 years ago, and I learn something new every day. On good days, I learn more than one thing."

Calisher was not directly involved in the original investigations of hantavirus pulmonary syndrome in 1993. However, shortly after the virus was identified, colleagues at the Centers for Disease Control and Prevention (CDC) asked him to try to determine the prevalence of the virus among rodents in Colorado. "Colorado is a large state and I am a little guy, so I reckoned I could not do that," he recalls. "Besides, I didn't have a truck, a trailer, or traps, didn't know one rodent from another, and had very little field experience."

Instead, he and his colleagues conducted long-term studies at three ecologically disparate sites. "We studied these sites for about 13 years and amassed a huge amount of data, more data than anyone had ever collected about hantaviruses and their rodent hosts, and published scores of papers," he says.



Calisher next developed an interest in bats. "Bats aren't rodents, of course, so all my previous experiences meant little, except for the perspective it gave me," he says. "Indeed, I am no bat expert. It was because my coauthors and I had never seen a proper review of bats and their viruses and because the SARS coronavirus had just been detected in bats that we were stirred to put together a review. We did not have direct experience, but we had the nerve to begin writing a review, trying at the beginning

Rabies and Other Viruses of Bats

Bat-borne rabies virus provides a classical example of how this remarkable host species helps to maintain and distribute this historically relevant disease just about everywhere except Australia. Thousands of individuals have captured and tested bats for rabies virus, and yet few isolated rabies virus from those animals. Astonishingly, although bats of so many species harbor rabies virus, many do so asymptomatically. Similarly, 10 viruses related to rabies virus of the family *Rhabdoviridae*, genus *Lyssavirus*, have been isolated from asymptomatic rodents and arthropods.

Australian bat lyssavirus (ABLV) was first isolated from a fruit bat—specifically, a black flying fox (*Pteropus alecto*), which was captured at Ballina, New South Wales, Australia in 1996. ABLV causes a fatal encephalitis in humans that is indistinguishable from that of classic rabies. Thus, analysis of ABLV changed how "rabies" is defined. Moreover, rabies human diploid cell vaccine protects against infection with ABLV. Due to the colonial nature of fruit bats, it is likely that ABLV will be found wherever such host bats congregate.

As with other vertebrates, simply finding antibody to a virus in a bat does not prove that the animal was infected with that virus or that it caused disease. Although detecting viral antigens or nucleic acids provides evidence for viral replication, isolating the virus proves it infected the animal. Even so, isolating virus from a bat does not indicate what role the bat plays in the natural cycle of that virus.

simply to prepare a list of viruses isolated from or detected in bats."

Calisher, a Yankees fan, grew up in New York City. His father was an automobile parts salesman, his mother a housewife. Neither his parents nor his sister was interested in science. However, he attended Stuyvesant High School, known for its focus on science. In 1958, he obtained a B.S. from the Philadelphia College of Pharmacy and Science in bacteriology, followed by a M.S. in gnotobiotics from the University of Notre Dame in 1961. In 1964, he earned a Ph.D. in microbiology at Georgetown University School of Medicine.

"I do not recall anything specific that spurred me to go into either science or microbiology except that I can never remember a time when nature did not interest me," he says. "I spent a great deal of time at the Museum of Natural History in New York City, but I spent a great deal more time playing baseball when I was growing up. To me, it doesn't matter whether one collects viruses, baseball rules, or postage stamps—yep, that too—collecting is collecting and one can learn a great deal from any of these hobbies."

During World War 2, Calisher's family spent summers on a farm in New Hampshire where he handled cattle, picked blueberries, and fished. "At the end of each summer's stay, I couldn't figure out why we were going back to New York City," he says. "It still doesn't make any sense to me. Now I live in Colorado at 8,500 feet. We have moose, elk, black-tailed deer, two species of rabbits, coyotes, Canada lynx, bobcats, and rodents of scores of species—plus a bat once in a while and, now that West Nile virus has swept away the non-immunes, lots of birds. It's like dying and going to heaven."

During a long career, Calisher studied many disease outbreaks, but two investigations stand out. In 1969, he traveled to Puerto Rico during a dengue epidemic. "It turned out that there were a million or more infections," he recalls. "That was an eye-opening experience." Two years later, he became involved in studying an epizoodemic of Venezuelan equine encephalitis that reached from northern South America to Texas. "That was the most remarkable summer of my career," he says. "I scarcely was able to get home to change clothes. There have been other epidemics, at other times and in other places, here and abroad, but these two were seminal for me."

Calisher and his wife, an experimental psychologist, have four children—two daughters and two sons—and eight grandchildren. He continues to indulge his main passions, family and baseball. He recently visited New York and Boston with one son and grandson, "watching baseball games, touring museums, and eating marvelous foods," he says. "It doesn't get any better than that."

Marlene Cimons
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At least 85 distinct viruses have been isolated or detected in bats via nucleic acid analysis (Table 1). Moreover, viruses have been detected in bats of about 85 of the 1,116 recognized species (some bats were not identified to species, some not even to genus). With the exception of rabies virus, few viruses have been isolated from bats of more than 3–4 species. Even rabies virus has distinct variants that circulate only among bats of certain species.

Several Viruses Emerged from Bats during the Past Few Decades

In September 1994, a horse trainer in Hendra, a suburb of Brisbane, Queensland, Australia, his stable hand, and most of his horses became ill with a respiratory syndrome. The trainer and 14 horses died, most of encephalitis, and all of these infections were attributed to a newly recognized paramyxovirus of the family *Paramyxoviridae*, genus *Henipavirus*, and designated Hendra virus, which was isolated from autopsy material.

Investigators failed to detect evidence of infection with Hendra virus in rodents, cats, dogs, goats, sheep, birds, or mosquitoes from the area. However, they did detect antibody to the virus in fruit bats (genus *Pteropus*), from which they later isolated infectious Hendra virus (Fig. 1). Subsequent cases of Hendra virus infection were observed in a farmer from Mackay (1995), a horse near Cairns (1999), and a human and a dead horse in northern Queensland (2004). These cases were coincident with the flying fox birthing season and with the local ripening of fruits on which such animals feed.

In 1997, local farmers and health officials observed deformed and stillborn piglets at a hog farm in New South Wales, Australia. The pregnancy rate and litter size at the farm decreased markedly as mummified fetuses increased. Serological evidence of infection was found among pigs at that and two nearby farms, in local flying foxes, and in mildly ill humans from the area. Investigators subsequently identified another paramyxovirus, called Menangle virus (genus *Rubulavirus*) that they isolated from fruit bats roosting near the farms. In 1999, a similar virus, Tioman virus (genus *Rubulavirus*), was isolated from fruit bats in Malaysia; it, too, can infect humans.

Separately, but also in Malaysia and Singapore during 1999, there was an outbreak of encephalitis and respiratory illness in pigs and in humans, leaving more than 250 adult men seriously ill, with more than 100 fatalities. Meanwhile, officials ordered the slaughter of more than 1 million pigs to control the outbreak. The etiologic agent proved to be yet another paramyxovirus, Nipah virus (genus *Henipavirus*), which is distantly related to Hendra virus. Nipah virus also is found in fruit bats (Fig. 2). Nipah virus also causes periodic outbreaks among humans in India and Bangladesh. Although contact with pigs was the principal means of transmission of Nipah virus to humans in Malaysia during the 1999 outbreak, in other countries it is more likely transmitted via fruit contaminated with excreta from virus-infected bats and by person-to-person contact.

The filoviruses Lake Victoria marburgvirus and the ebolaviruses cause devastating hemorrhagic fevers. However, despite intensive efforts, the reservoir hosts of these viruses remained unidentified for many years. Recently, investigators detected RNA corresponding to that of the Lake Victoria marburgvirus and of Zaire ebolavirus in tissues of asymptomatic bats. Specifically, marburgvirus RNA was found in tissues of insectivorous bats of three species and in tissues of fruit bats collected in a mine where workers and others in the vicinity succumbed to an outbreak of Marburg hemorrhagic fever. Antibody to the virus was detected in bat sera, but investigators failed to isolate the virus. In Gabon, fruit bats yielded Zaire ebolavirus RNA sequences that closely matched those found in humans during Ebola hemorrhagic fever outbreaks at the Gabon–Congo border. Again, efforts to isolate the virus proved unsuccessful. Some experts speculate that filoviruses are arthropod-borne or plant viruses, with non-blood-feeding arthropods somehow transmitting the virus to intermediate hosts such as bats or to humans.

FIGURE 1



Mother and pup gray-headed flying foxes (*Pteropus poliocephalus*), a host of Hendra virus, Menangle virus, rabies virus, Australian bat lyssavirus, and Nelson Bay virus. (Photo courtesy of Vivien Jones, Bellingen, New South Wales, Australia.)

SARS Virus Traced to Bats

In November 2002 a deadly respiratory illness, severe acute respiratory syndrome (SARS), arose in southeastern China and then spread rapidly to 29 countries. The epidemic involved more than 8,000 people, killing 774 of them before coordinated efforts to isolate and quarantine patients brought it to an end in July 2003.

FIGURE 2



Variable flying fox (*Pteropus hypomelanus*), a host of Nipah virus. (Photo © 2007, J. Epstein, Consortium for Conservation Medicine, New York, N.Y.)

Investigators identified the etiologic agent as a coronavirus new to humans, and called it SARS-CoV (family *Coronaviridae*, genus *Coronavirus*). Epidemiologic studies suggested that the early cases of SARS were associated with the wildlife meat industry in China. Molecular virologists then detected SARS–CoV RNA in fecal and respiratory specimens from masked palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*) in exotic meat markets. Later, investigators recognized that palm civets are incidental hosts, rather than reservoir hosts of the virus.

The reservoirs of a diverse group of SARS-CoV-like coronaviruses in Southeast Asia appear to be bats of several closely related species of Chinese horseshoe-nosed bats (suborder Microchiroptera, family Rhinolophidae) (Fig. 3). Intensive efforts to identify the reservoir(s) of SARS-CoV led to the discovery of many diverse coronaviruses in bats of various species, some related to known coronavirus pathogens of humans, animals and birds, and others in new and distinct phylogenetic groups. In some caves, the prevalence of antibody to SARS-CoV in apparently healthy horseshoe bats was as high as 84%.

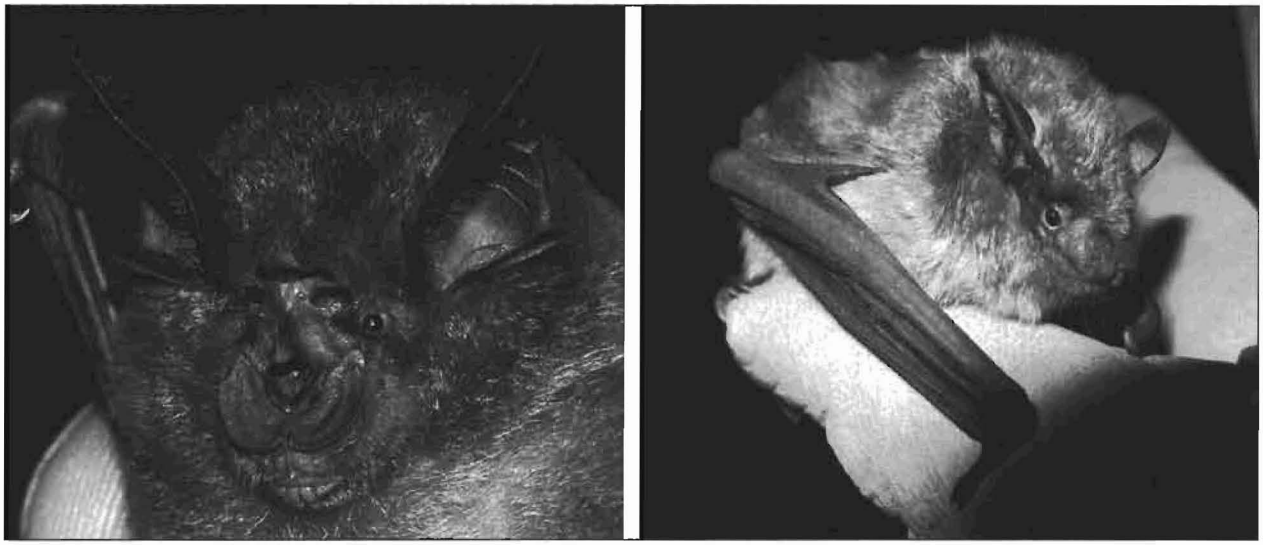
However, no one has isolated an infectious coronavirus from such bats. Because coronaviruses are found in bats from both eastern and western hemispheres, but no bat species inhabits both hemispheres, it is likely that coronaviruses coevolved with their bat hosts. Many bats have both RNA of SARS-CoV-like viruses in their feces and antibodies to those viruses, suggesting that bats may be persistently infected with coronaviruses, probably without overt disease. The molecular mechanisms that allow persistent coronavirus infection of bats in the absence of disease are not understood.

Viruses Evade Bat Immune Systems

Some viruses manage to evade the immune response of their reservoir host (reservoir hosts for certain viruses are not persistently infected), causing persistent but asymptomatic infections before being transmitted to hosts of other species. To do so, some viruses encode factors that enable them to evade host immune responses. Although immune evasion mechanisms are recognized in persistent viruses of humans and animals such as mice and rats, no such factor has yet been identified in viruses of bats. Immune evasion mechanisms likely are virus-specific rather than generally immunosuppressive. For example, big brown bats (*Eptesicus fuscus*) and little brown bats (*Myotis lucifugus*) are susceptible to infections with the St. Louis encephalitis and Japanese encephalitis flaviviruses. Moreover, these viruses persist when the bats hibernate, and they develop viremia when they are aroused from hibernation. These observations suggest that bats maintain and disseminate these viruses in enzootic and epizootic foci. Other viruses infect bats, causing viremia and also triggering antibody production.

Viruses such as hantaviruses and arenaviruses,

FIGURE 3



(Left panel) Chinese rufous horseshoe bat (*Rhinolophus sinicus*), a host of a severe acute respiratory syndrome (SARS) coronavirus. (Photo courtesy of Gareth Jones, School of Biological Sciences, Bristol University, Bristol, U.K.) (Right panel) Big brown bat (Eptesicus fuscus), host of a newly recognized coronavirus in North America. (Photo by Paul Cryan.)

which infect rodents but not bats, also may adapt by minimizing pathology in their reservoir hosts while causing pathologies in their incidental (human) hosts, in which different immune systems yield strong responses that clear the virus but contribute to host pathology. The outcome of such an infection in an alternative host sometimes can prove disastrous for both host and virus.

Research into bat immunology has not revealed conspicuous differences between bats and other mammals. Bats have bone marrow, innate immunity, and produce antibodies, T cells, and cytokines. While hundreds of monoclonal antibodies are available for studying human and mouse immunoproteins, they are not likely to be useful for studying bat immune responses because of the substantial evolutionary distances between members of these taxa. However, bat genome sequences can be analyzed to detect genes that likely regulate immune responses.

The genome of the little brown bat is being sequenced at the Broad Institute in Boston. This analysis will speed the development of assays to follow bat gene expression in response to viral infection. Additional reagents can then be developed to use with other bat species, including those that harbor zoonotic viruses. Understanding how viruses manipulate bat immune responses will provide valuable insights into viral ecology and pathogenesis.

Why Bat Viruses Are Emerging

Until recently, bats were seldom considered likely hosts by experts seeking emerging viruses. Most viruses from bats were discovered almost accidentally, while testing other vertebrates and inadvertently captured bats. Meanwhile, humans continue to encroach on natural areas, exposing ourselves and our domesticated animals to viruses that earlier lacked opportunities to jump to them. As we disrupt those areas, converting them into farmland or extracting minerals and petroleum from them, we alter habitats, while also perturbing interactions between viruses and hosts.

Traditionally, researchers who studied bats found themselves dispelling detrimental misconceptions about their subjects. Perhaps seeking to avoid further criticisms of bats, ongoing public relations efforts led such researchers away from studying bat ecology as it relates to infectious diseases. Moreover, few investigators with expertise about bats also are knowledgeable about viruses, and vice

versa. Those who are poised to study those viruses face other impediments, including the need to develop or procure bat-specific reagents and cell cultures. To complicate those efforts, experts go to great lengths to overcome the secretive nature of bats and the fact that bats of certain species are endangered. In facing such challenges, cooperation among researchers from different disciplines and backgrounds brings mutual benefits.

Until recently, pathogen discovery was either the result of studies during an epidemic of unrecognized cause or an incidental occurrence. Although surveys that are not associated with disease outbreaks are expensive, they can reveal novel viruses. Knowing that bats are reservoir hosts of virulent viruses affecting humans, livestock, and wild animals provides ample reason to conduct broad surveys of bat populations. They might even lead to discoveries of new pathogens and to strategies for preventing diseases.

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