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Recent recognition of bats as reservoir hosts of emerging viruses

Charles H. CALISHER, Ph.D., prof.

Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado, USA

Bats (order Chiroptera, suborders Megachiroptera (»flying foxes«) and Microchiroptera) are abundant, diverse, and have been found on all continents except Antarctica. Although bats provide us with certain resources and many feed on insects, many populations of bats are at risk, threatened or endangered. The characteristics of these mammals include particular diets, colonial or solitary nature, ability to fly, cyclic migrations and daily movement patterns, the ability to enter torpor or to hibernate, long life span, roosting behaviors, a unique capacity to echolocate and, critically, their susceptibility to viruses make them suitable hosts of viruses, bacteria, parasites, fungi, and other disease agents. Although bats of certain species have long been known to transmit Rabies virus, they have been only rarely studied as hosts of viruses. Recent outbreaks and epidemics of newly recognized human and livestock diseases caused by bat-transmitted viruses have attracted the interest of scientific investigators to these mammals. This review summarizes germane facts regarding the characteristics of bats and provides information regarding 66 viruses that have been isolated from them. The literature on the biology of bats is abundant with respect to narrowly defined characters, including echolocation, diet, and distribution, but it is deficient with respect to bat biology in general. In addition, it is clear that bat conservation policies are inadequate and that we have merely begun to scratch the surface of a field of discovery regarding the roles of bats in disease emergence.

Key words

bats
fruit bats
flying fox
emerging viruses
reservoir host

Nova saznanja o šišmišima kao nosiocima novootkrivenih virusa

Šišmiši (red Chiroptera, podred Megachiroptera – (»leteće lisice«) i Microchiroptera) su mnogobrojni, raznoliki sisavci koji se nalaze na svim kontinentima svijeta osim Antarktika. Iako šišmiši imaju korisnu ulogu u prirodi, mnogi se hrane insektima, brojne vrste šišmiša su danas ugrožene. Karakteristike ovih sisavaca uključuju određenu prehranu i život u kolonijama ili samostalno, mogućnost letenja, cikličke migracije i svakodnevno tipično letenje, sposobnost ulaska u stanje mirovanja (torpor ili hibernacija), dugotrajan životni ciklus, boravak u skrovištima, jedinstvena sposobnost eholokacije, njihova prijemljivost na viruse čini ih pogodnim domaćinima za viruse, ali i za bakterije, parazite, gljive i razne druge uzročnike bolesti. Iako su šišmiši određenih vrsta već otprije bili poznati po mogućnosti prenošenja virusa bjesnoće, rijetko su bili proučavani kao domaćini drugih virusa. Nedavne pojave i epidemije novih prepoznatih bolesti u ljudi i životinja uzrokovani virusima koje prenose šišmiši privukli su zanimanje znanstvenika za ove sisavce. Ovaj pregled donosi osnovne podatke o njihovim srodnim karakteristikama te informacije o 66 virusa izoliranih u šišmiša. Postoji brojna literatura o biologiji šišmiša koja se odnosi na njihov usko definirani karakter, uključujući mogućnost eholokacije, prehranu i rasprostranjenost, ali je oskudna što se tiče opće biologije šišmiša. Također je jasno da su zakoni o zaštiti šišmiša neadekvatni te da smo tek započeli proučavati jedno neotkriveno područje uloge šišmiša u pojavnosti nekih bolesti.

Ključne riječi

šišmiši
šišmiši koji se hrane voćem
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rezervar domaćin

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Introduction

In about the past decade, and with increasing regularity, it has become apparent that the volant mammals, bats and flying foxes (order Chiroptera), harbor a surprising number of viruses. The recognition of this observation has led to a surge in publications concerning original observations and reviews on the subject [1–15]. It is a wonder that this group of mammals had been overlooked for so long because of the more than 4,600 recognized species of mammals 1116 are bats [16]. Bats of the order Chiroptera are grouped into two suborders, Megachiroptera, containing a single subfamily, Pteropodidae (42 genera, comprising 186 species), and Microchiroptera, containing 17 bat families (160 genera, comprising 930 species) [17]. Indeed, of all vertebrates, bats may be the most abundant, diverse, and geographically dispersed, being found on all continents except Antarctica. Bats are no more alike than are rodents or birds and, while much is known about them, detailed information is lacking in regard to the remarkable variations of their anatomy, life styles, roles in ecosystems ecology, and importance as reservoir hosts of viruses of proven or potential significance for human and veterinary health. Depending on the species, bats have wings-pans of 130 mm to 2 m. Some feed on insects, others on mammals, fish, blood, fruit, or pollen. Nearly all bats can echolocate to navigate and to find prey, and bat echolocation and signal processing have provided models for sonar systems [18]. Although there seems to be a negative public perception of bats (rabies, vampirism (including classic very old movies), bats becoming tangled in women's hair and other myths), they are crucial to all terrestrial biotic communities in that they assist in controlling insects, reseed cut forests, and pollinate plants that provide food for humans and others, and their feces (guano) is used as fertilizer and for manufacturing soaps, gasohol, and antibiotics [19]. Due to these misperceptions about bats and excess concern about rabies (Bats of only three species (*Diphylla ecaudata* (Hairy-legged vampire bat), *Diaemus youngi* (White-winged vampire bat) and *Desmodus rotundus* (Vampire bat)) are known vampires and involved in transmission of Rabies virus; available evidence indicates that only the Vampire bat is important in this respect [20]), there have been systematic efforts to reduce or eliminate bat populations, with serious consequences regarding insect control and crop production, without coincidental reduction in the already low incidence of Rabies virus transmission by bats [21].

For many years viruses had been isolated from bats, but these occurrences, with few exceptions, were incidental to collections of birds for attempted isolations of viruses from them. The fact that viruses were isolated from one or two of the few bats captured should have suggested that the overall prevalence of viruses in bats was high, but it did not. In addition, most methodical studies of the natural histories of bats and their importance as reservoir hosts of zoonotic viruses were underfunded, except those regarding the roles of bats in maintaining and transmitting Rabies virus. Recently, however, these remarkable creatures have been shown to be the reservoir hosts of a many viruses causing disease in humans or livestock, sometimes in both.

This paper provides a summary of data regarding viruses isolated from bats but is limited in scope because of space constraints. For example, although there is substantial serologic evidence for infection of bats with many viruses, this review we will focus only on the 66 viruses that have been isolated from or detected in bat tissues (Table 1) and on the roles of bats in maintaining and transmitting viruses. For additional information about the evolution and phylogeny of bats, their ability to fly and migrate, their tendency to enter torpor or to hibernate (potentially important in maintaining viruses), their life spans, their population characteristics and roosting behaviors, their ability to echolocate, how little is known about antibody and cytokine synthesis in bats and many other aspects of immune functioning of bats, [see reference 4]. Also, there is little evidence that these viruses affect bats. On the contrary, most bats from which viruses have been isolated or in whose tissues viruses have been detected have not been described as sick; the exception is Rabies virus. Nearly half of apparently healthy bats from a roost in Texas known to house Rabies virus-infected bats had neutralizing antibody to Rabies virus, suggesting acquired immunity following prior exposure [22]. Co-evolution of bat viruses and their bat hosts is a distinct possibility.

Viruses found in bats

Detecting a virus in a bat (or in anything else) does not indicate that that virus replicates in the bat, that the bat is an important reservoir host of the virus, that the virus is transmissible to humans (zoonoses) or other vertebrates, that it causes disease, or that the virus is arthropod-borne. Many more studies are needed to confirm and extend any of these observations. Table 1 lists many viruses isolated from or detected in bats, but it is not known whether the presences of these viruses simply were incidental occurrences or have significance. However, when a disease outbreak is shown to have been caused by a virus detected solely or principally in bats, correlation is an intriguing possibility. This paper provides brief scenarios regarding five relatively recently detected viruses from bats and the diseases those viruses cause.

Australian bat lyssavirus

In 1996, a lyssavirus (Australian bat lyssavirus, family *Rhabdoviridae*, genus *Lyssavirus*) was isolated from tissues of an encephalitic Black flying fox (*Pteropus alecto*) found near Ballina, New South Wales, Australia [23]. Six months later, a bat handler from Rockhampton, Queens-

Table 1. A summary of 66 viruses from bats of various species, listed by virus families and genera
Tablica 1. Pregled 66 virusa izoliranih iz različitih vrsta šišmiša prema rodu i porodici virusa

Family	Genus	Viruses
Arenaviridae	*Arenavirus*	(1) Tacaribe virus
Bunyaviridae	*Orthobunyavirus*	(3) Catu, Guama and Nepuyo viruses
	Hantavirus	(1) Hantaan virus
	Phlebovirus	(2) Rift Valley fever and Toscana viruses
	unassigned	(2) Kaeng Khoi and Bangui viruses
Coronaviridae	*Coronavirus*	(1) SARS coronavirus*
Flaviviridae	*Flavivirus*	(17) Bukalasa bat, Carey Island, Central European encephalitis, Dakar bat, Entebbe bat, Japanese encephalitis, Jugra, Kyasanur Forest disease, Montana Myotis leucoencephalitis, Phnom-Penh bat, Rio Bravo, St. Louis encephalitis, Saboya, Sokuluk, Tamana bat, Uganda S and Yokose viruses
Herpesviridae	unassigned	(3) Agua Preta, Parixa viruses and a cytomegalovirus
Orthomyxoviridae	*Influenzavirus A*	(1) Influenza A virus
Papillomaviridae	unnamed	(1) virus unnamed
Paramyxoviridae	*Henipavirus*	(2) Hendra and Nipah viruses
	Rubulavirus	(3) Mapuera, Menangle and Tioman viruses
	undetermined	(1) an unidentified paramyxovirus
Picornaviridae	undetermined	(1) Juruaca virus
Reoviridae	*Orbivirus*	(3) Fomede, Ife and Japanaut viruses
	Orthoreovirus	(3) Broome, Nelson Bay and Pulau viruses
Rhabdoviridae	*Lyssavirus*	(10) Aravan, Australian bat lyssavirus, Duvenhage, European bat lyssavirus 1, European bat lyssavirus 2, Irkut, Khujand, Lagos bat, Rabies and West Caucasian bat viruses
	unassigned	(4) Gossas, Kern Canyon, Mount Elgon bat and Oita 296 viruses
Togaviridae	*Alphavirus*	(3) Chikungunya, Sindbis, Venezuelan equine encephalitis viruses
Unclasifield	–	(4) Issyk-kul (=Keterah), Kasokero, Mojui dos Campos and Yogue viruses

* SARS coronavirus is but one of many coronaviruses that have now been detected in bats. Although efforts have only recently begun, and have focused solely on coronaviruses, many newly recognized coronaviruses have been detected in Asia and North America. This very likely is the start of the beginning of the dawn of a new era in virology and natural history.

land, Australia developed numbness and weakness in her arm and later died from encephalitis. She had been infected with Australian bat lyssavirus. Two years later, a woman from Mackay (Queensland, Australia) was diagnosed with Australian bat lyssavirus infection at her death, two years after having been bitten by a sick bat [24]. Rabies human diploid cell vaccine is useful for prophylaxis against this virus, clearly a close relative of classical Rabies virus. Serologic evidence suggests that this virus also is present in bats in Thailand and, because of the colonial nature of many bats, it is likely that this virus may be found wherever the host bats are found.

Henipaviruses

In 1994 an acute respiratory illness occurred in one human and 14 horses in Hendra, a suburb of Brisbane, Queensland, Australia. In all, 21 horses and 2 humans (a trainer and a stable hand) were infected and the trainer died [25]. Other outbreaks occurred in 1994, 1999 and 2000, infecting five horses and two humans, and killing all but one human [26].

Hendra virus (family *Paramyxoviridae*, genus *Henipavirus* (named after Hendra virus and (see below) Nipah virus)) was shown to be the etiologic agent of this disease. The natural hosts and probable reservoirs of Hendra virus are fruit bats (»flying foxes«) of the genus *Pteropus*, including the Black flying fox , Gray-headed flying fox (*P. poliocephalus*), Little red flying fox (*P. scapulatus*) and Spectacled flying fox (*P. conspicillatus*). Little is known about the dynamics of infection in flying foxes and how Hendra virus infection is maintained in them.

Nipah virus, a paramyxovirus related to Hendra virus, was first isolated in 1999 from pigs and adult human males with fever and encephalitis, some with respiratory illness, during a major outbreak in peninsular Malaysia, and then in Singapore [27]. Of 265 reported human cases, 105 (40%) were fatal. Direct contact with infected pigs was identified as the predominant mode of human infection and most of the human cases in the Malaysian outbreak had a history of direct contact with live pigs. In addition, most were adult male Chinese pig farmers, which essentially ruled out an arthropod-borne virus disease. More than one million pigs were culled to contain the outbreak; a costly and heart-breaking disaster. With the knowledge that *Pteropus* species bats were the likely reservoir of the closely related Hendra virus in Australia, the Large flying fox (*Pteropus vampyrus*) and the Variable flying fox (*P. hypomelanus*) soon were found to be natural and reservoir hosts for Nipah virus [28].

Since 2001, sporadic outbreaks of human Nipah virus-associated disease have been identified in Bangladesh. These cases were not associated with pigs, and there was some evidence suggesting human-to-human transmission. Serologic surveys of domestic and wild animals in Bangladesh provided evidence of Nipah virus infection only in Indian flying foxes (*Pteropus giganteus*). Serologic surveillance of Indian flying foxes in India in 2003 found that 54% had neutralizing antibodies to Nipah virus (J. H. Epstein, et al., personal communication, 2006), suggesting that Nipah virus or a closely related virus was widespread across the range of Indian flying foxes and in 2001 Nipah virus infections in humans in India were detected. Neutralizing antibodies to Nipah virus have been detected in Large flying foxes in Indonesia and Cambodia, and the virus was isolated from Lyle's flying fox (*Pteropus lylei*) in Cambodia. Thus, the henipaviruses likely occur across the entire global distribution of pteropid bats [29].

Two other paramyxoviruses have been isolated from bats. Menangle virus (family *Paramyxoviridae*, genus *Rubulavirus*) was isolated in 1997 from stillborn piglets at a large commercial piggery near Menangle, New South Wales, Australia [30]; the bat colony and the piggery had co-existed for 29 years before the incident. Fetal deaths, abortions, teratogenic defects, non-suppurative myocarditis and hepatitis also occurred or were present in some piglets. Two of 250 humans in contact with the infected pigs had high titers of antibodies to Menangle virus and both reported a febrile illness with a measles-like rash; neither had direct exposure to flying foxes. Bats living seasonally in a large, mixed colony of Grey-headed flying foxes and Little red flying foxes and roosting within 200 m of the affected piggery had neutralizing antibodies to Menangle virus, as did flying foxes of other species from other colonies thousands of kilometers distant and previous to the outbreak at Menangle (H. E. Field, unpublished data). Menangle virus was not isolated from flying foxes, paramyxovirus-like virions labeled with antibody to Menangle virus from a convalescent sow were seen by electron microscopy in flying fox feces collected beneath the roost near the piggery.

Tioman virus, a rubulavirus distinct from Menangle virus, has been isolated from Variable flying foxes in Malaysia. Little is known about the host range or pathogenesis of this newly recognized paramyxovirus [31].

SARS – coronavirus-like viruses of bats

In 2002, a previously unrecognized coronavirus (family *Coronaviridae*, genus *Coronavirus*) was recognized as causing a new, severe acute respiratory syndrome (SARS) in humans [32]. This virus, named Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), is a distant relative of the group 2 coronaviruses that infect rodents, cattle, dogs, pigs and humans, and has been assigned to group 2b. It is distinct from other coronaviruses recently identified in bats in southern China.

The earliest cases of SARS were associated with wildlife meat (»wet markets«) and a survey of wildlife in a southern Chinese market recovered SARS-CoV-like viruses from wild vertebrates brought to market for human consumption. Under wet market circumstances, immune responses to persistent virus infections could have been reduced, virus shedding increased and susceptible animals might have become infected and shed viruses. Many clues were accrued but these were, for the most part, dead-ends.

Recently, several groups have essentially simultaneously identified bats from different locations in southern China as being infected with SARS-CoV-like viruses or had antibody to these newly recognized coronaviruses, including bats of several species of Chinese horseshoe bats (suborder Microchiroptera, family *Rhinolophidae*, genus *Rhinolophus*) [33, 34]. The prevalence of antibody to bat SARS-CoV in some species of Chinese horseshoe bats was as high at 84%. Pathology has not yet been associated with SARS-CoV infection of bats.

Subsequently collected data show that the virus responsible for the 2002–2003 outbreak most likely originated from this group of bat-associated viruses. Antibody against SARS-CoV-like viruses of bats was also detected in Leschenault's rousette (*Rousettus leschenaultia*), a cavedwelling megachiropteran, suggesting that fruit bats also may support infection with SARS-CoV-like viruses. Thus, the natural history of SARS-CoV appears to involve a previously unrecognized SARS-CoV-like virus of bats being transmitted in meat markets to amplifying hosts including Masked palm civets, Raccoon dogs and a Hog badger, and then spilling over to infect humans in close contact with these intermediate hosts or their tissues. Subsequent human-to-human transmission of the virus was associated with adaptive mutations in the viral genome [39].

The general theme running through all these events is that there is no evidence that the bats from which these viruses came were anything but healthy. Available evidence suggests that these are ancient viruses that have long circulated in their bat hosts. We should ask what event or series of events precipitated the apparent recent emergences of these viruses. Are there identifiable environmental factors that altered bat ecology and facilitated the movement of these zoonotic agents beyond their natural ecological niches? In addition to the presence of the disease agent, disease emergence requires a bridge from the natural host to a susceptible spillover host. Such bridges may be caused by changes to the agent, to the host, or to the environment. Data on fruit bats of many species suggest that their populations are in decline, primarily as a result of habitat loss and hunting. We can hypothesize that bat populations under stress, having altered foraging and behavioral patterns, supplemented by virus niche expansion or alteration, may move to within closer proximity to humans and livestock. Chong et al. [35] suggested that the risk of humans contracting infection of Nipah virus from bats is low. Once it escapes its natural cycle, however, its epidemiologic characteristics may be changed considerably.

Filoviruses

Although not yet proven there is increasing evidence that ebolaviruses may be bat-borne. Five viruses have been placed in the taxon *Filoviridae*. Four of them (Ebola Zaire virus, Ebola Sudan virus, Ebola Ivory Coast virus and Ebola Reston virus) comprise the genus *Ebolavirus*; Lake Victoria marburgvirus is the sole member of the genus *Marburgvirus*. The natural reservoir hosts of these viruses have not yet been identified. However, experimental infections of Angola free-tailed bats (*Mops condylurus*), Little free-tailed bats (*Chaerephon pumilus*) and Wahlberg's epauletted fruit bats (*Epomophorus wahlbergi*) with Ebola Zaire virus led to replication of virus in these bats [36]. Recently, fragments of RNA identical to fragments of ebolaviral RNA were detected in liver and spleen tissues of three fruit bats: Hammer-headed fruit Bat (*Hypsignathus monstrosus*), Franquet's epauletted Bat (*Epomops franqueti*), and Little collared fruit bat (*Myonycteris torquata*) [37]. Ebolavirus-specific immunoglobulin M antibody was detected in bats of the same species, but ebolaviral RNA was not detected in bats with antibody and antibody was not detected in bats with ebolaviral RNA.

Irrespective of the fascinating nature of these findings, unless an ebolavirus (or a marburgvirus) is isolated from a wild vertebrate, unless experimental infections demonstrate that virus is shed by an individual of that species, and unless that disease can be transmitted under controlled conditions, these findings will remain merely intriguing and promising. Monath has postulated that there may be an as yet undetected ebolavirus, one that is non-pathogenic but which may give rise to pathogenic genotypes by mutation and that the filoviruses may be arthropod or plant viruses [38].

Future directions and needs

Why are we surprised when a new disease is discovered and the causative agent of that disease is discovered shortly afterwards. »Oh«, we say, »imagine that. I never would have believed such a thing could occur«. Then we go back to »business as usual«, without expanding our horizons. Recognition of a zoonotic virus is always precipitated by human, livestock or wildlife deaths, with considerable associated distress and economic cost. We wonder how such a virus could have evaded detection, why it had not been seen to cause disease before, and whether it is a new virus or merely a newly discovered virus, whether an »enemy« has intentionally imposed it upon us. These are natural occurrences of nature but what, really, do we know about nature? Not much, seems to me.

An important method to predict emergence of zoonotic diseases that has been overlooked repeatedly is the natural history survey, followed by studies of species of interest identified through the survey. Longitudinal prospective field studies, expensive and therefore not often funded these days, could be predictive. Studies of hantaviruses in the southwestern U.S. [39] have helped epidemiologists and public health officials make recommendations to reduce the risk of infection and to help forecast the location and severity of future outbreaks of hantavirus pulmonary syndrome. However, the etiologic agent of that disease is now known. What of the many, perhaps tens of thousands of viruses, which have not been discovered? Surveying bats may be as potentially a fruitful a place to begin as any. It is likely that further emphasis on greater prioritization of such studies might be shown to be very cost-effective in the long run.

Recognize that the 66 viruses (11 virus families) listed in Table 1 have been isolated from or detected in bats of 78 of the 1,116 recognized species of bats. **No viruses have been detected in bats of 1,038 species.** Go forth and detect!

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