

Emerging Viruses: Coming in on a Wrinkled Wing and a Prayer

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The role that bats have played in the emergence of several new infectious diseases has been under review. Bats have been identified as the reservoir hosts of newly emergent viruses such as Nipah virus, Hendra virus, and severe acute respiratory syndrome-like coronaviruses. This article expands on recent findings about bats and viruses and their relevance to human infections. It briefly reviews the history of chiropteran viruses and discusses their emergence in the context of geography, phylogeny, and ecology. The public health and trade impacts of several outbreaks are also discussed. Finally, we attempt to predict where, when, and why we may see the emergence of new chiropteran viruses.

*The bat is dun with wrinkled wings
Like fallow article,
And not a song pervades his lips,
Or none perceptible.
His small umbrella, quaintly halved,
Describing in the air
An arc alike inscrutable,
Elate philosopher!
Deputed from what firmament
Of what astute abode,
Empowered with what malevolence
Auspiciously withheld.
To his adroit Creator
Ascribe no less the praise;
Beneficent, believe me,
His eccentricities.*

—Emily Dickinson

Despite recognizing their eccentricities, Emily Dickinson could

not have predicted the scientific interest bats would generate for centuries to come. Bats have long been recognized as hosts for viruses but, for many years, were associated only with rabies virus. Scientists then turned to these flying mammals as potential reservoirs of new and emerging viruses. In 1974, Sulkin and Allen [1] listed infections with alphaviruses, flaviviruses, arenaviruses, paramyxoviruses, reoviruses, rhabdoviruses, and a suite of nonclassified viruses. Both suborders within the order Chiroptera were represented: Microchiroptera (microbats) and Megachiroptera (megabats, including flying foxes and fruit and

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blossom bats). In 2006, Calisher et al. [2] updated this comprehensive list of viruses isolated from bats. Many viruses were serendipitously isolated as part of field surveillance work, and for most viruses, bats did not feature in the known epidemiology of the disease that the viruses cause. Among reservoirs for the genus *Lyssavirus*, family Rhabdoviridae, bats are well represented. Perhaps it is to be expected that, in the genus in which the type species is the archetypal bat virus, rabies virus, all related viruses (with the exception of Mokola virus) have been isolated from bats. The other families in which bats are well represented as reservoirs include the Flaviviridae and the Bunyaviridae. In the genus *Flavivirus*, Rio Bravo virus group, all original isolates are from bats. In total, 18 flaviviruses and 12 bunyaviruses have been isolated from bats, but only 7 of these are considered medically important viruses (among flaviviruses, Japanese encephalitis virus, Kyasanur Forest disease virus, St. Louis encephalitis virus, and West Nile virus; and among bunyaviruses, Hantaan virus, Rift Valley fever virus, and Toscana virus), and the role that bats play in the epidemiology of the diseases that they cause is not believed to be significant. Interest in bats was renewed at the end of the 20th century, when during <5 years, 5 new viruses belonging to the order Mononegavirales were discovered (figure 1). All of these viruses appeared to have bats as a reservoir host, and 3 of these, Australian bat lyssavirus, Hendra virus, and Nipah virus, caused serious human disease. Most recently, bats have been identified as the reservoir host of serious acute respiratory syndrome (SARS) virus-like coronaviruses [3] (figure 1). Additionally, some researchers speculate that bats may also be the reservoir host for Ebola virus [4]. Here we expand on recent findings about bats and viruses and their relevance to human infections, beginning with a brief history of chiropteran virology.

LESSONS IN HISTORY

When discussing the role of bats as reservoir hosts, there have been 3 main phases of virological discovery.

When scientists first identified a link between bats and viruses. During 1906–1908, in the state of Santa Catarina in southern Brazil, ~4000 cattle and 1000 horses and mules died of paralytic rabies. During daylight hours, bats were observed approaching animals and trying to bite them. Carini [5] suspected that these bats were involved in the transmission of the rabies virus. Haupt and Rehaag, 2 German veterinarians who were called to investigate the outbreaks, could prove the presence of Negri bodies in the brain of captured bats, and this resulted in the first proven causal link between bats and viral disease [1]. It was not until the rabies virus was isolated from an insectivorous bat in the United States in 1953 that investigators began to focus their attention on this flying mammal as a possible reservoir host for this virus in nature. At this time,

investigators also began to consider that bats may be reservoir hosts for other viruses.

When scientists went into the forest. During the early 1950s, the Rockefeller Foundation and several governmental agencies embarked on programs to find viruses that caused encephalitis and tropical fevers [6]. They established and supported field laboratories in many tropical countries, fostering the concept of broad-based surveys of arthropods, wildlife, do-

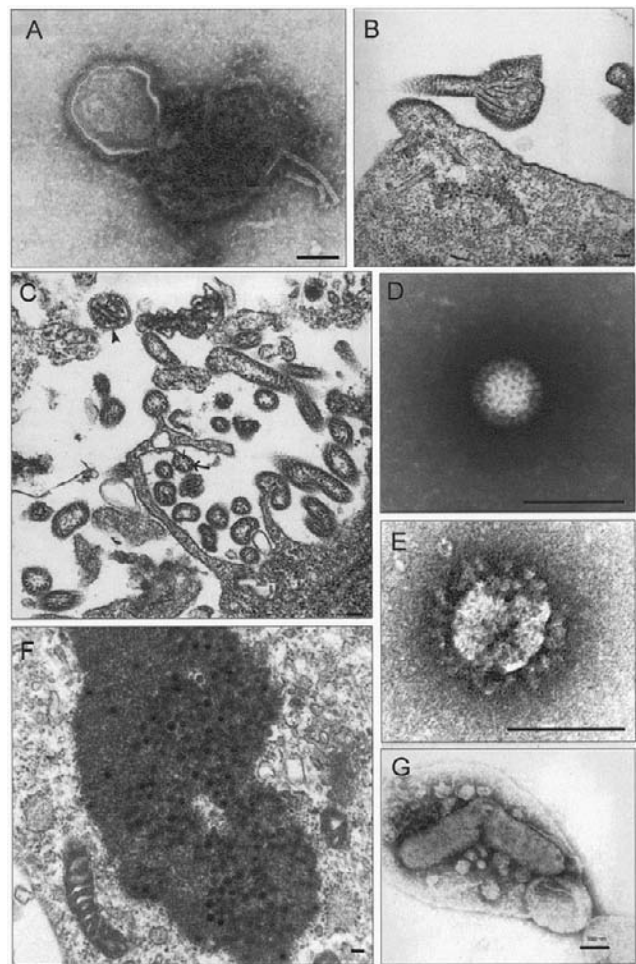


Figure 1. Electron micrographs of some recently discovered bat viruses. *A*, Negative contrast image of Hendra virus representative of the order Mononegavirales, family Paramyxoviridae, subfamily Paramyxovirinae, genus *Henipavirus*. *B*, Ultrathin section of Nipah virus representative of the order Mononegavirales, family Paramyxoviridae, subfamily Paramyxovirinae, genus *Henipavirus*. *C*, Ultrathin section of Tioman virus, order Mononegavirales, family Paramyxoviridae, subfamily Paramyxovirinae, genus *Rubulavirus*; arrows, viruses; arrowhead, surface projections. *D*, Negative contrast image of Pulau virus, family Reoviridae, genus *Orthoreovirus*. *E*, Negative contrast image of severe acute respiratory syndrome virus-like coronavirus representative of the order Nidovirales, family Coronaviridae, genus *Coronavirus*. *F*, Ultrathin section of Pulau virus, family Reoviridae, genus *Orthoreovirus*. *G*, Negative contrast image of Australian bat lyssavirus, order Mononegavirales, family Rhabdoviridae, genus *Lyssavirus*. Bars, 100 nm.

mestic animals, and patients. These surveys saw the registration of many new viruses, including some isolated from bats.

When bats came out of the forest. The role that bats may play in harboring viruses was revisited in the 1990s. A new paramyxovirus, Hendra virus, was responsible for the deaths of 2 humans and 15 horses during 2 separate outbreaks [7]. After extensive epidemiological investigations, it was determined that fruit bats, namely those belonging to the genus *Pteropus*, were the most likely reservoir hosts. Shortly thereafter, this new virus was isolated from a number of pteropid bats [8]. During these investigations, a new rhabdovirus, Australian bat lyssavirus, was isolated from a pteropid bat [9]. When another 2 RNA viruses were discovered as part of disease outbreak investigations, authorities immediately looked to bats as possible reservoir hosts. Menangle virus was responsible for a large number of fetal deaths at a commercial piggery, and antibodies capable of neutralizing Menangle virus have been found in pteropid bats [10]. Nipah virus swept through numerous piggeries in Malaysia and killed >100 people during the period from 1998 through 1999. Local pteropid bats were identified as having antibodies capable of neutralizing Nipah virus, and eventually the virus was isolated from bat excreta in Malaysia [11]. In Bangladesh, >70 people have been killed in annual Nipah virus outbreaks since 2001, and once again, local pteropid bats have been identified as having antibodies capable of neutralizing Nipah virus [12–14]. The natural history and pathogenesis of Hendra virus and Nipah virus is reviewed by Daszak et al. [15] and Field et al. [16]. During investigations of Nipah virus in Malaysia, 2 previously unrecognized viruses, Tioman virus and Pulau virus, were isolated from bat excreta [17, 18] (figure 1). More recently, although civets were originally implicated in the SARS outbreak in China, the true wildlife reservoir was found to be bats, which are also sold in wet markets [3]. During <10 years, 7 new RNA viruses were isolated from bats in Southeast Asia and Australia. Different species of bats with different geographic ranges were implicated.

LESSONS IN GEOGRAPHY

Generally speaking, the geographic distribution of a virus is limited by the geographic distribution of its reservoir host, whereas the geographic distribution of a viral disease is a result of the combined effect of the reservoir host's distribution, the location of the spillover host (or hosts), and the environment in which they are brought together. This is clearly demonstrated with the recently emerged paramyxoviruses. To date, Hendra virus, isolated from the Australian species of pteropid bats, has been responsible for disease only in spillover hosts (horses) on the east coast of Australia. All human infections have occurred as a result of exposure to infected horses—thus, the limited geographic distribution of human disease. The Malaysian strain of Nipah virus, isolated from Malaysian species of pteropid

bats, has caused disease only in spillover hosts (the major one being pigs) in that country, and, similarly, human infections occurred as a result of exposure to infected pigs. The Bangladesh strain of Nipah virus has caused disease only in spillover hosts (humans) in that region. In all of these examples, if the reservoir host was not afforded the opportunity of coming in contact with the spillover host, human disease would not have ensued.

Typically, anthropogenic factors lead to alterations of contact rates between humans, domestic animals, and wildlife hosts [19]. The major cause of infectious disease emergence can be linked to human activities [19]. Examples include agricultural expansion into pristine forests, as occurred in Malaysia where Nipah virus emerged; wildlife trade, in which many species of animals are brought together at high density with humans, which led to the emergence of SARS in China; or global travel, during which people can expand the range of a virus by carrying it on planes, which led to the global spread of SARS. If one were to try to predict spillover events, it would be prudent to focus on the geographic range of the reservoir host. Changes in this range may create new opportunities for the virus, particularly if this change results in the reservoir host coming in contact with a suitable spillover host. Bat phylogeny and viral phylogeny may also suggest where we may see new viruses emerge.

LESSONS IN PHYLOGENY

If one examines the viruses isolated from bats and the bat species from which they were isolated, one would detect that some closely related bats harbor closely related viruses. For example, an orthoreovirus (Nelson Bay virus) was recovered from a grey-headed flying fox (*Pteropus poliocephalus*) in eastern Australia [20]. Although no diseases have been associated with this virus, interest has been rekindled by the isolation of 2 related orthoreoviruses from flying foxes in different geographic locations. Pulau virus was isolated in Malaysia from *Pteropus hypomelanus*, and Broome virus was isolated from *Pteropus alecto* in northern Australia [18] (Cummins, Lunt, and Wang, personal communication). Although the bat orthoreoviruses are currently not considered to have any zoonotic potential, they are examples of viruses evolving in geographically separated bat populations (figure 2). The phylogeny of these bats and their associated viruses supports the theory of viral coevolution with their chiropteran hosts. This theory is further supported by the isolation of new paramyxoviruses and lyssaviruses isolated from bats in Australia and Southeast Asia (figure 3) and the large number of coronaviruses found in various bats at different locations in China [21, 22]. These patterns of similar—yet distinct—viruses in similar—yet distinct—species of bats preempts the discovery of “new” chiropteran viruses.

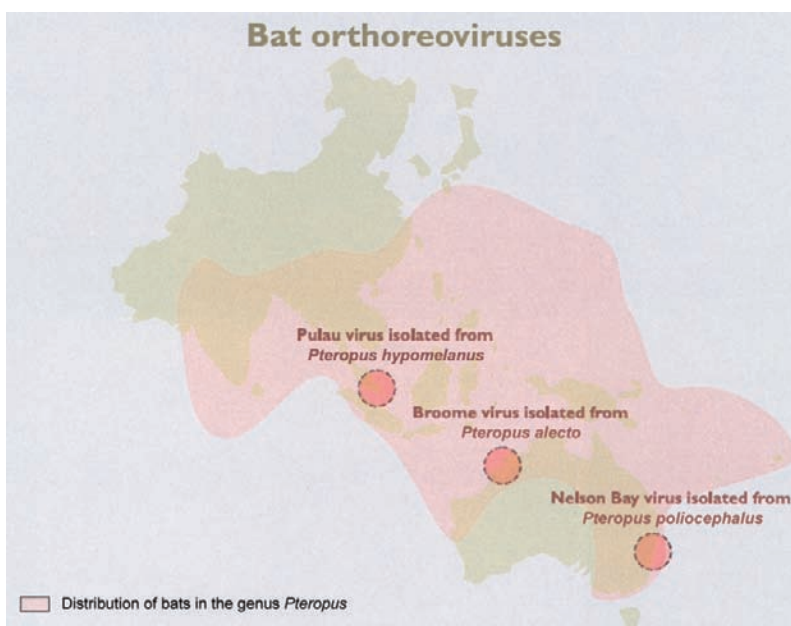


Figure 2. Bat orthoreoviruses: viruses belonging to the genus *Orthoreovirus*, family Reoviridae, isolated from bats belonging to the genus *Pteropus*, family Pteropodidae. Nelson Bay virus was isolated from *Pteropus poliocephalus* in Nelson Bay, New South Wales, Australia [20]. Broome virus was isolated from *Pteropus alecto* in Broome, Western Australia (Cummins, Lunt and Wang, personal communication). Pulau virus was isolated from *Pteropus hypomelanus* on Tioman Island, Malaysia [18].

With regard to the lyssaviruses, one can take the example beyond the bat genus level. Although there appears to be little genetic variation among Australian bat lyssavirus isolates within the genus *Pteropus* throughout Australia, isolates from insectivorous bats (*Saccolamus flaviventris*) are sufficiently different to group in a second clade [23]. One explanation for this is that when chiropteran divergence took place millions of years ago, each suborder took with it its own variant of Australian bat lyssavirus.

LESSONS IN ECOLOGY

Disease ecology concerns the study of the interactions between hosts and pathogens at a range of levels. Although recent work has made progress of understanding bat-virus interactions at the molecular and individual host level, we are still in our infancy when it comes to understanding how these interactions play out at the population and ecosystem levels. Consider the 4 viruses that emerged from pteropid bats within 5 years: Hendra virus, Nipah virus, Menangle virus, and Australian bat lyssavirus. The fact that 4 viruses emerged from 1 host genus within a short period of time strongly suggests that host factors play a role in emergence. However, unraveling the ecological changes that caused emergence requires a detailed understanding of how host biology interacts with the rapidly changing ecosystems on which these bats depend. For bat diseases, this is generally an immense challenge. Bats have historically been underappreciated by both the general public and the scientific

community, and therefore, basic data on bat disease ecology and immunology are lacking. Furthermore, bats have incredibly complex population structures and are highly mobile, nocturnal, and often difficult to catch. They also exhibit some unique life-history traits that may influence their interactions with viruses in ways that we do not yet understand. For example, bats are the only mammals that fly, they have very short digestive tracts, they have unusual dietary preferences, and many species hibernate.

Despite these challenges, some researchers have made progress in understanding the causes of spillover of emerging bat diseases. Hendra virus researchers used a modeling framework to show that habitat fragmentation may change the dynamics of Hendra virus infection within *Pteropus* species, leading to increased risk of emergence among horses and humans [24]. In other cases, observational and epidemiological studies have been able to identify putative causes of emergence. For example, there is evidence that planting fruit trees around piggeries caused increased bat and pig contact in Malaysia, leading to the spillover of Nipah virus to pigs [15]. With this knowledge, appropriate controls can be implemented to prevent future spillover events. In Queensland, Australia, advice to horse owners includes placing horses in paddocks that do not contain trees attractive to bats for either feeding or roosting. In addition, horse feed bins or watering points should not be placed under trees when there is a risk of bats using that tree for feeding, resting, or roosting.

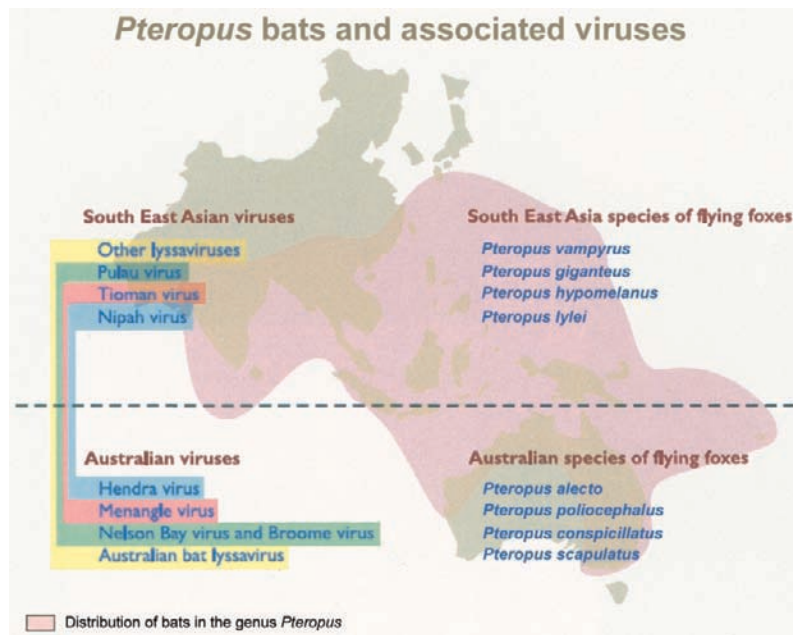


Figure 3. Pteropus bats and associated viruses: viruses isolated from bats in Southeast Asia and the closely related viruses isolated from bats in Australia. Also listed are some of the *Pteropus* species found in these different regions. Note that this list is not exhaustive, and some species of bats can be found in both regions.

LESSONS IN PUBLIC HEALTH AND TRADE

The outbreak of Nipah virus infection in Malaysia was devastating in terms of human morbidity and mortality and the country's economy. During the outbreak, there were 265 human cases with 105 fatalities. The outbreak also resulted in the slaughter of >1 million pigs, causing a loss of ~60% of Malaysian pig farms and 36,000 jobs [19]. The costs to the Malaysian economy associated with the destruction of pigs, the closure of farms, the loss of trade of pigs, and the decrease in consumption of pork was estimated to be ~US\$350 million, and the additional cost to the government from subsidies, revenue loss, and controlling the outbreak was estimated to be in the vicinity of US\$275 million [25]. In India and Bangladesh, where there have been 6 outbreaks of Nipah virus infection during a period of 5 years, a total of 123 people have died, with case-fatality rates among outbreaks of 37.5%–75% [13, 14, 26]. The economic impacts of these outbreaks has not been assessed.

The effects of the SARS outbreak were more widespread. This outbreak resulted in >8000 cases of probable SARS and 774 deaths worldwide [27]. The direct and indirect costs of controlling the SARS outbreak in 1 hospital alone in Canada amounted to CDN\$12 million [28]. The high case-morbidity rate and the lack of a cure affected trade, travel, and societal interactions. The overall economic cost of the SARS epidemic worldwide has been estimated to be ≥US\$30 billion [29].

Since 1996, there have been only 2 human deaths caused by

Australian bat lyssavirus infection [30]. This has resulted in recommendations for the use of rabies vaccine to protect people occupationally exposed to the virus and as a postexposure treatment for humans bitten or scratched by a bat, giving rise to an unprecedented ongoing cost to the government [31].

THE RESERVOIR HOST

The single most interesting aspect of most viral infections in bats is the apparent lack of host response to established infection, a characteristic synonymous with the profile of a reservoir host. Viruses isolated in the field have predominantly come from healthy bats, except for bats infected with lyssaviruses. Experimental infection with many viruses, including Hendra virus and Nipah virus, is nonpathogenic in bats, and seroconversion rates vary.

The question remains whether we are witnessing an increase in emergence of bat viruses or becoming more vigilant and efficient with surveillance and detection of viruses. After examining the statistics, Dobson [32] concluded that bats are not overrepresented in the numbers of pathogens that emerge from them, because <2% of human pathogens have bats as natural reservoirs [33]. Of all human pathogens, the bat virus that should cause the most concern is still the first one that came to our attention—rabies virus and the related lyssaviruses. This is the only group of viruses for which there is a well-documented causal link between direct contact with an infected (rabid) bat and human (or other terrestrial host) infection.

Humans can develop rabies after direct contact with a rabid bat; however, the greater threat to global human health is from rabid terrestrial hosts, because the vast majority (95%–98%) of human rabies deaths worldwide occur in regions in which canine rabies is endemic [34].

CONCLUSIONS

In this third phase of virological discovery, bats have become more visible both in a physical sense and in terms of their reservoir host status. Why have the bats come out of the forest? Deforestation, which results in habitat destruction, roost disturbance, and habitat fragmentation, is undoubtedly the main force driving bats into urban and periurban areas [35]. Ecosystem and land-use changes have played a significant role in the emergence of new, and reemergence of old, infectious diseases in humans (e.g., malaria, yellow fever, hemorrhagic fevers, dengue fever, cholera, and West Nile virus) [36]. Forests have effectively disappeared in 25 countries, and >90% of the former forest cover has been lost in a further 29 countries [36]. Increasing consumption per person, multiplied by a growing human population, is stated as the root cause of the increasing demand for ecosystem services that has led to these losses [36]. Continued degradation and fragmentation of the natural habitats of microbats and megabats has forced increased overlap of bat, domestic animal, and human ecologies, which has created increased opportunities for bat-borne zoonotic diseases to emerge.

Today, we sit on the cusp of a new era of understanding of the emergence of viruses, and much of this understanding will come when our understanding of the reservoir hosts expands. It is envisaged that phylogenetic analyses of viruses and their hosts will define the evolutionary relationships and origins of viruses and provide the link between the reservoir hosts' ecology and viral epidemiology. Only through these investigations, and a greater understanding and appreciation of the complex biology and behavior of bats, will the role that bats have played in the evolution of viruses be fully realized.

As Calisher et al. [2] predict, other bat-associated viral diseases will be discovered, and some may be pathogenic to humans. There are clues as to which viruses we can expect to find and where they may be found. But to move toward prediction and ultimately prevention of emergence of zoonotic diseases from bats, future research must aim to improve our understanding of the immunology of bats, the dynamics of pathogen cycles within bat populations, and the nature of interaction among bats, humans, and domestic animals.

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