

# Bats: Important Reservoir Hosts of Emerging Viruses

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## INTRODUCTION

The remarkable mammals known as “bats” and “flying foxes” (order Chiroptera [“hand wing”]) may be the most abundant, diverse, and geographically dispersed vertebrates (Table 1). Although a great deal is known about them, detailed information is needed to explain the astonishing variations of their anatomy, their lifestyles, their roles in ecosystems ecology, and their importance as reservoir hosts of viruses of proven or potential significance for human and veterinary health.

Bats fly with wings which range in span from 130 mm to 2 m. Bats of various species feed on insects, mammals, fish, blood, fruit, and pollen. Bats of most species echolocate to navigate and to find prey. Bats are found on all continents except Antarctica. Bats also are being increasingly recognized as reservoir hosts for viruses which can cross species barriers (i.e., “spill

over”) to infect humans and other domestic and wild mammals. Nonetheless, studies of the natural histories of bats and their importance as reservoir hosts of zoonotic viruses largely have been underappreciated and underfunded, except for their role in maintaining and transmitting rabies virus. Irrespective of the negative public perception of bats, they are critical elements of all terrestrial biotic communities. They help control insects, reseed cut forests, and pollinate plants that provide food for humans and other species, and their guano is used as a fertilizer and for manufacturing soaps, gasohol, and antibiotics (21, 69, 83). Bat echolocation and signal processing have provided models for sonar systems (112, 130).

Myths and misunderstandings about the roles of bats in ecosystems and their danger to other species as hosts of rabies virus have led to efforts to extirpate bat populations, with serious consequent effects on insect control and crop production, without coincidental reduction in the already low incidence of rabies virus transmission by bats (93).

This paper summarizes what is known about viruses isolated from bats. Although there is serologic evidence for infection of bats with many viruses (see, for example, references 82 and 101), we will focus here only on the 66 viruses that have been

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TABLE 1. Species of bats (order Chiroptera), by family and genus

Family and subfamily	No. of genera	No. of species
Megachiroptera, Pteropodidae	42	186
Microchiroptera		
Craseonycteridae	1	1
Emballonuridae	13	51
Furipteridae	2	2
Hipposideridae	9	81
Megadermatidae	4	5
Molossidae	16	100
Mormoopidae	2	10
Mystacinidae	1	2
Myzopodidae	1	1
Natalidae	3	8
Noctilionidae	1	2
Nycteridae	1	16
Phyllostomidae	56	160
Rhinolophidae	1	77
Rhinopomatidae	1	4
Thyropteridae	1	3
Vespertilionidae	47	407

isolated from or detected in bat tissues (Table 2) and the roles of bats in maintaining and transmitting viruses. Some of these bat-borne viruses can cause diseases of humans and other animals. The roles played by bats in the maintenance and transmission of viruses require consideration of the unique characteristics that distinguish bats from all other mammals. Examples are drawn from the extensive literature on rabies virus in bats, as well as from recent data on the roles of bats in the natural cycles of other viruses.

### Evolution and Phylogeny of Bats

Whereas other mammals, such as certain species of rodents (order Rodentia) and carnivores (order Carnivora), may possess traits in common with species of bats, such as the ability to hibernate, no group of mammals shares the full suite of attributes that make bats unique. Of the more than 4,600 recognized species of mammals, 925 (about 20%) are bats (147). Bats are grouped into two suborders: Megachiroptera, containing a single family, Pteropodidae (42 genera, comprising 166 species), and Microchiroptera, containing 16 bat families (135 genera, comprising 759 species) (Table 1) (138).

Bats evolved early and have changed relatively little in comparison with mammals of other taxa (69). Although the fossil record of bat evolution is incomplete (77), a recent analysis of 17 nuclear genes dated the origin of chiropterans to the Eocene period (52 to 50 million years ago), coincident with a significant rise in global temperature (147). Three major microchiropteran lineages were traced to Laurasia and a fourth to Gondwana (147). The correspondingly ancient origins deduced for certain zoonotic viruses maintained in bats, such as the henipaviruses (60) and lyssaviruses (10), suggest a long history of cospeciation. Viruses that evolved with bats may have used for replication cellular receptors and biochemical pathways which are conserved in mammals that evolved later and which underwent radiation in later geological periods. If so, these conserved cellular receptors and pathways could enhance the capacity for transmission of bat-associated viruses to other mammals.

### Ability To Fly

Bats are unique among mammals in their ability to fly. Bats fly daily in pursuit of food, and bats of many species fly long distances during seasonal migrations (62). For example, bats of *Myotis* spp. may travel 200 to 400 miles from their winter hibernation sites (reviewed in reference 62), and Mexican free-tailed bats (*Tadarida brasiliensis mexicana*) migrate at least 800 miles between their summer caves in Texas and New Mexico and their overwintering sites in Mexico (36) and are otherwise very widely distributed. In France, rabies virus infections have been associated with the migratory routes of Nathusius' pipistrelle (*Pipistrellus nathusii*) bats (20). Silver-haired bats (*Lasiurus noctivagus*) seasonally range from Alaska, across Canada, and south to Texas (13). Rabies virus variants associated with silver-haired bats and the Eastern pipistrelle (*Pipistrellus subflavus*) have been identified from numerous locations throughout the geographic range of these bats (106, 124), and the same variants have been identified as the cause of the majority of cases of indigenously acquired human rabies in the United States and Canada (127).

Different patterns of migration within the same species of bat, as occurs with relatively solitary species, such as the silver-haired bat (69), and colonial cave-dwelling species, such as Mexican free-tailed bats (128), may permit exchange of novel viruses or virus variants between migrating and nonmigrating subpopulations of conspecifics or bats of other species. A Mexican free-tailed bat infected with a rabies virus variant normally associated with hoary bats (*Lasiurus cinereus*), suggests interspecies transmission (124). In the field, rabid bats of one species have been observed to be aggressive toward bats of other species (14). Moreover, Shankar et al. (136), in a study of the phylogenesis of divergence of rabies viruses from bats and terrestrial animals in Colorado, found that bats of different species had the same genotypic variants, indicating active interspecies transmission of rabies virus. They concluded that, at least in Colorado, animal rabies occurs principally in bats and that identification of bat-associated variants of rabies viruses in domestic cats, gray foxes (*Urocyon cinereoargenteus*), and striped skunks (*Mephitis mephitis*) demonstrates the importance of rabies virus spillover from bats to domestic and terrestrial wild vertebrates.

### Torpor and Hibernation

An important trait of temperate bats of the families Vespertilionidae and Rhinolophidae is their ability to enter into daily torpor and seasonal hibernation to conserve energy during cool nights and winter months (89). The impact of torpor and hibernation on the pathogenesis and maintenance of viral infections in bats has not been studied extensively. However, viruses may overwinter in bats, and persistently infected bats may shed viruses, such as lyssaviruses (family *Rhabdoviridae*) or flaviviruses (family *Flaviviridae*) for extensive periods without evidence of disease (143). Virus isolation and antibody studies suggest that many viruses can cause persistent infections in bats (82).

When big brown bats (*Eptesicus fuscus*) and little brown bats (*Myotis lucifugus*) were experimentally infected with Japanese encephalitis virus (JEV) and then subjected to temperatures

TABLE 2. Viruses isolated from naturally-infected bats worldwide

Virus	Bat species (common name) <sup>a</sup>
Family <i>Rhabdoviridae</i> , genus <i>Lyssavirus</i>	
Rabies virus.....	Numerous bat species, essentially worldwide
Lagos bat virus.....	<i>Eidolon helvum</i> (African straw-colored fruit bat), <i>Micropteropus pusillus</i> (Peters' lesser epauletted fruit bat), <i>Epomops dobsonii</i> (Dobson's epauletted fruit bat), <i>Nycteris gambiensis</i> (Gambian slit-faced bat), <i>Epomophorus wahlbergi</i> (Wahlberg's epauletted fruit bat)
Duvenhage virus.....	<i>Miniopterus</i> sp., <i>Nyctalus noctula</i> (noctule), <i>Vespertilio murinus</i> (particolored bat), <i>Nycteris thebaica</i> (Egyptian slit-faced bat)
Australian bat lyssavirus.....	Megachiroptera (multiple <i>Pteropus</i> spp.), Microchiroptera sp. from Australia, <i>Saccolaimus flaviventris</i> (yellow-bellied pouched bat)
European bat lyssavirus 1.....	<i>Eptesicus serotinus</i> (common serotine), <i>Rousettus aegyptiacus</i> (Egyptian rousette)
European bat lyssavirus 2.....	<i>Myotis myotis</i> (mouse-eared myotis), <i>Myotis dasycneme</i> (pond myotis), <i>Myotis nattereri</i> (Natterer's myotis), <i>Miniopterus schreibersii</i> (Schreibers' long-fingered bat), <i>Rhinolophus ferrumequinum</i> (greater horseshoe bat), <i>Myotis daubentonii</i> (Daubenton's myotis)
Aravan virus.....	<i>Myotis blythii</i> (lesser mouse-eared myotis)
Khujand virus.....	<i>Myotis mystacinus</i> (whiskered myotis)
Irkut virus.....	<i>Murina leucogaster</i> (greater tube-nosed bat)
West Caucasian bat virus.....	<i>Miniopterus schreibersii</i> (Schreibers' long-fingered bat)
Family <i>Rhabdoviridae</i> , genus unassigned	
Gossas virus.....	<i>Tadarida</i> sp.
Kern Canyon virus.....	<i>Myotis yumanensis</i> (Yuma myotis)
Mount Elgon bat virus.....	<i>Rhinolophus eloquens</i> (eloquent horseshoe bat)
Oita 296 virus.....	<i>Rhinolophus cornutus</i> (little Japanese horseshoe bat)
Family <i>Orthomyxoviridae</i> , genus	
<i>Influenzavirus A</i> , influenza A virus.....	<i>Nyctalus noctula</i> (noctule)
Family <i>Paramyxoviridae</i> , genus <i>Henipavirus</i>	
Hendra virus.....	<i>Pteropus alecto</i> (black flying fox), <i>Pteropus poliocephalus</i> (gray-headed flying fox), <i>Pteropus scapulatus</i> (little red flying fox), <i>Pteropus conspicillatus</i> (spectacled flying fox)
Nipah virus.....	<i>Pteropus hypomelanus</i> (variable flying fox), <i>Pteropus vampyrus</i> (large flying fox), <i>Pteropus lylei</i> (Lyle's flying fox)
Family <i>Paramyxoviridae</i> , genus <i>Rubulavirus</i>	
Mapuera virus.....	<i>Sturnira lilium</i> (yellow epauletted bat)
Menangle virus.....	<i>Pteropus poliocephalus</i> (gray-headed flying fox)
Tioman virus.....	<i>Pteropus hypomelanus</i> (variable flying fox)
Family <i>Paramyxoviridae</i> , genus	
undetermined, a parainfluenzavirus.....	<i>Rousettus leschenaultia</i> (Leschenault's rousette)
Family <i>Coronaviridae</i> , SARS coronavirus.....	
	<i>Rhinolophus sinicus</i> (Chinese horseshoe bat), <i>Rhinolophus pearsonii</i> (Pearson's horseshoe bat), <i>Rhinolophus macrotis</i> (big-eared horseshoe bat), <i>Rhinolophus ferrumequinum</i> (greater horseshoe bat)
Family <i>Togaviridae</i> , genus <i>Alphavirus</i>	
Chikungunya virus <sup>b</sup> .....	<i>Scotophilus</i> sp., <i>Rousettus aegyptiacus</i> (Egyptian rousette), <i>Hipposideros caffer</i> (Sundevall's leaf-nosed bat), <i>Chaerephon pumilus</i> (little free-tailed bat)
Sindbis virus.....	Rhinolophidae sp., Hipposideridae sp.
Venezuelan equine encephalitis virus.....	<i>Desmodus rotundus</i> (vampire bat), <i>Uroderma bilobatum</i> (tent-making bat), <i>Artibeus phaeotis</i> (pygmy fruit-eating bat)
Family <i>Flaviviridae</i> , genus <i>Flavivirus</i>	
Bukalasa bat virus.....	<i>Chaerephon pumilus</i> (little free-tailed bat), <i>Tadarida condylura</i> (Angola free-tailed bat)
Carey Island virus.....	<i>Cynopterus brachiotis</i> (lesser short-nosed fruit bat), <i>Macroglossus minimus</i> (lesser long-tongued fruit bat)
Central European encephalitis virus.....	Unidentified bat
Dakar bat virus.....	<i>Chaerephon pumilus</i> (little free-tailed bat), <i>Taphozous perforatus</i> (Egyptian tomb bat), <i>Scotophilus</i> sp., <i>Mops condylurus</i> (Angola free-tailed bat)
Entebbe bat virus.....	<i>Chaerephon pumilus</i> (little free-tailed bat), <i>Mops condylurus</i> (Angola free-tailed bat)
Japanese encephalitis virus.....	<i>Hipposideros armiger terasensis</i> (great roundleaf bat; also known as Formosan leaf-nosed bat), <i>Miniopterus schreibersii</i> (Schreibers' long-fingered bat), <i>Rhinolophus cornutus</i> (little Japanese horseshoe bat)
Jugra virus.....	<i>Cynopterus brachiotis</i> (lesser short-nosed fruit bat)
Kyasanur Forest disease virus.....	<i>Rhinolophus rouxi</i> (rufous horseshoe bat), <i>Cynopterus sphinx</i> (greater short-nosed fruit bat)
Montana myotis leucocephalitis virus.....	<i>Myotis lucifugus</i> (little brown bat)
Phnom-Penh bat virus.....	<i>Eonycteris spelaea</i> (lesser dawn bat), <i>Cynopterus brachiotis</i> (lesser short-nosed fruit bat)

Continued on following page

TABLE 2—Continued

Virus	Bat species (common name) <sup>a</sup>
Rio Bravo virus.....	<i>Tadarida brasiliensis mexicana</i> (Mexican free-tailed bat), <i>Eptesicus fuscus</i> (big brown bat)
St. Louis encephalitis virus.....	<i>Tadarida brasiliensis mexicana</i> (Mexican free-tailed bat)
Saboya virus.....	<i>Nycteris gambiensis</i> (Gambian slit-faced bat)
Sokuluk virus.....	<i>Vespertilio pipistrellus</i> (probably <i>Pipistrellus pipistrellus</i> ; common pipistrelle)
Tamana bat virus.....	<i>Pteronotus parnellii</i> (Parnell's mustached bat)
Uganda S virus.....	<i>Rousettus</i> sp., <i>Tadarida</i> sp.
Yokose virus.....	Unidentified bat
Family <i>Bunyaviridae</i> , genus <i>Bunyavirus</i>	
Catu virus.....	<i>Molossus obscurus</i> (possibly <i>Molossus currentium</i> ; Thomas' mastiff bat)
Guama virus.....	Unidentified bat
Nepuyo virus.....	<i>Artibeus jamaicensis</i> (Jamaican fruit-eating bat), <i>A. lituratus</i> (great fruit-eating bat)
Family <i>Bunyaviridae</i> , genus <i>Hantavirus</i> ,	
Hantaan virus.....	<i>Eptesicus serotinus</i> (common serotine), <i>Rhinolophus ferrumequinum</i> (greater horseshoe bat)
Family <i>Bunyaviridae</i> , genus <i>Phlebovirus</i>	
Rift Valley fever virus.....	<i>Micropteropus pusillus</i> (Peters' dwarf epauletted fruit bat), <i>Hipposideros abae</i> (Aba leaf-nosed bat), <i>Miniopterus schreibersii</i> (Schreibers' long-fingered bat), <i>Hipposideros caffer</i> (Sundevall's leaf-nosed bat), <i>Epomops franqueti</i> (Franquet's epauletted bat), <i>Glauconycteris argentata</i> (common butterfly bat)
Toscana virus.....	<i>Pipistrellus kuhlii</i> (Kuhl's pipistrelle)
Family <i>Bunyaviridae</i> , genus unassigned	
Kaeng Khoi virus.....	<i>Chaerephon plicatus</i> (wrinkle-lipped free-tailed bat)
Bangui virus.....	<i>Scotophilus</i> sp., <i>Pipistrellus</i> sp., <i>Tadarida</i> sp.
Family <i>Reoviridae</i> , genus <i>Orbivirus</i>	
Ife virus.....	<i>Eidolon helvum</i> (straw-colored fruit bat)
Japanaut virus.....	<i>Syconycteris australis</i> (southern blossom bat)
Fomede virus.....	<i>Nycteris nana</i> (dwarf slit-faced bat), <i>Nycteris gambiensis</i> (Gambian slit-faced bat)
Family <i>Reoviridae</i> , genus <i>Orthoreovirus</i>	
Nelson Bay virus.....	<i>Pteropus poliocephalus</i> (gray-headed flying fox)
Pulau virus.....	<i>Pteropus hypomelanus</i> (variable flying fox)
Broome virus.....	<i>Pteropus alecto</i> (black flying fox)
Family <i>Arenaviridae</i> , Tacaribe virus.....	
	<i>Artibeus lituratus</i> (great fruit-eating bat), <i>A. jamaicensis</i> (Jamaican fruit-eating bat)
Family <i>Herpesviridae</i> , genus unassigned	
Agua Preta virus.....	<i>Carollia subrufa</i> (gray short-tailed bat)
A cytomegalovirus.....	<i>Myotis lucifugus</i> (little brown bat)
Parixa virus.....	<i>Lonchophylla thomasi</i> (Thomas' nectar bat)
Family <i>Picornaviridae</i> , genus undetermined,	
Juruaca virus.....	Unidentified bat
Unclassified	
Issyk-kul (Keterah virus) <sup>c</sup> .....	<i>Nyctalus noctula</i> (noctule), <i>Eptesicus serotinus</i> (common serotine), <i>Pipistrellus pipistrellus</i> (common pipistrelle), <i>Myotis blythii</i> (lesser mouse-eared myotis), <i>Rhinolophus ferrumequinum</i> (greater horseshoe bat), <i>Scotophilus kuhlii</i> (lesser Asiatic yellow house bat), <i>Cynopterus brachyotis</i> (lesser short-nosed fruit bat), <i>Eonycteris spelaea</i> (lesser dawn bat), <i>Chaerephon plicatus</i> (wrinkle-lipped free-tailed bat), <i>Hipposideros diadema</i> (diadem leaf-nosed bat), <i>Taphozous melanopogon</i> (black-bearded tomb bat), <i>Rhinolophus lepidus</i> (Blyth's horseshoe bat), <i>Rhinolophus horsfeldi</i> (possibly <i>Megaderma spasma</i> , lesser false vampire bat)
Mojui dos Campos virus.....	Unidentified bat
Yogue virus.....	<i>Rousettus aegyptiacus</i> (Egyptian rousette)
Kasokero virus.....	<i>Rousettus aegyptiacus</i> (Egyptian rousette)

<sup>a</sup> Species names and common names are given according to N. B. Simmons (138) and other sources.

<sup>b</sup> Arthropod-borne viruses (arboviruses) isolated from or detected in bats likely were transmitted to them by arthropods, whether from another individual of that bat species (reservoir host) or from another vertebrate reservoir host. With few exceptions, e.g., rabies virus, relatively little is known about the natural history of these viruses or about non-arthropod-transmitted viruses of bats.

<sup>c</sup> Issyk-Kul and Keterah viruses may be synonyms.

likely to be encountered during hibernation (8 to 24°C), individuals maintained viremias for 95 to 108 days (143). Virus titers in the blood of bats maintained at 24°C were equal to peak viral titers at temperatures at which the bats were active.

Perhaps cold temperatures suppress immune responses that might otherwise control viremia. Bats transferred from 8°C to 24°C 9 weeks after inoculation with JEV had transient viremias followed by the rapid development of significant antiviral an-

tibody titers. Nevertheless, the fact that infectious JEV was recovered from seropositive bats 15 weeks after the shift in temperature indicated that infection persisted (143). It is possible that neutralizing antibody has a shorter half-life in bats than in other mammals. Tick-borne encephalitis virus and other viruses have been isolated from bats with neutralizing antibody, and bats are susceptible to reinfection with tick-borne encephalitis viruses (82).

High titers of virus were obtained from brown fat of apparently healthy bats inoculated with rabies virus when the bats were kept at low temperatures (4, 142, 143). Vampire bats (*Desmodus rotundus*) that survive challenge with rabies virus may excrete virus in their saliva (1). Rabies virus was isolated from big brown bats that were captured to establish colonies and then died in the first month of captivity (135). Antiviral antibodies were detected in sera of several apparently healthy bats born in the new colony, suggesting past or subclinical rabies virus infection (135). Mexican free-tailed bats may transmit rabies virus transplacentally, as evidenced by the fact that infectious virus was isolated from cell lines established from fetal tissues of these bats (141). Studies of Mexican free-tailed bats roosting at a colony in Austin, Texas, identified rabies virus in about 70% of several hundred downed, dead, or dying bats, which represented a relatively small proportion of the estimated 600,000 bats in that colony. Over the study's 2-year duration, about 45% of apparently healthy bats from this roost were found to have neutralizing antibody to rabies virus, suggesting acquired immunity following prior exposure (101; C. Rupprecht [U.S. Centers for Disease Control and Prevention, Atlanta, Ga.], personal communication, 2006). Because only one or another of many methods usually is applied in studies of rabies virus in bats, we do not know the proportion of bats having both viral RNA in their tissues and antibody to rabies virus.

Temperate and tropical bats of the family Molossidae appear to be transitional between true hibernating bats and tropical bats that have limited ability to enter torpor. For example, the Western bonneted bat (*Eumops perotis*) enters a period of daily torpor during the winter that is similar to the daily hibernation or torpor that occurs in temperate zone bats during the summer (89).

### Long Life Span

The extreme longevity of bats, together with the possibility that they might develop persistent infections with certain viruses, may help maintain the viruses and transmit them to other vertebrates. Many species of small temperate bats of the suborder Microchiroptera have life spans that exceed 25 years, with the greatest longevity, of 35 years, documented for a little brown bat. (On average, little brown bats weigh about 7 g.) This extreme longevity in a small mammal places bats well outside the traditional regression line for mammals that relates the life expectancy (9) to the ratio of metabolic rate to body weight (see reference 44, Fig. 45).

If bats routinely become persistently infected by certain viruses, and infectivity lasts for months or possibly years, the impact on the basic reproductive number of infection ( $R_0$ ) would be significant.  $R_0$  is the expected number of newly infected hosts that one infectious host will produce during its

period of infectiousness in a large population of completely susceptible individuals (65). Since  $R_0$  is the sum of the products of the average duration of infection, the average contact rate between infectious and susceptible individuals, and the probability of transmission per contact between an infectious and a susceptible individual, increased duration of infectiousness or increased prevalence of infection in a population can dramatically enhance the potential for secondary infections that emanate from a single infected individual. Persistent viral infections occurring among long-lived bats, coupled with their often gregarious roosting behavior, could greatly increase the potential for intra- and interspecies transmission of viruses.

### Population Size and Roosting Behavior

The frequently great population densities of bats and their crowded roosting behavior increase the likelihood of intra- and interspecies transmission of viral infections. Bats are the most abundant of mammals, and except for humans and perhaps rodents, they are the most widely distributed land mammals (154). Certain species of bats, such as Mexican free-tailed bats, are highly gregarious and roost in southwestern caves of the United States, such as Carlsbad Caverns and Frio Cave, in densely packed aggregates of approximately 300 bats per ft<sup>2</sup> (37), in populations comprising several million individuals (37, 94). Under these conditions the only example of airborne rabies virus transmission was documented, either in droplets of excreta or by small particle aerosol (38, 155).

### Bat Population Structure

The demographic and spatial structuring of bat populations is sufficiently variable to offer opportunities for viruses that cause both acute and persistent infections to be maintained. The potential for migratory and nonmigratory populations to serve as a mixing vessel for viruses has already been mentioned. Additionally, within given regions, bat populations may be panmictic or may exist as metapopulations, offering the potential for seasonal virus transmission and annual outbreaks of viral diseases as well as the potential for periodic outbreaks among spatially discrete populations.

Colonial microchiropterans (such as Schreibers' long-fingered bat, *Miniopterus schreibersii*, and Mexican free-tailed bats) typically exist in panmictic populations of hundreds of thousands or millions of individuals and produce an annual birth pulse (37). In theory, such large bat populations could sustain acute viral infections that produce permanent sterilizing immunity in affected individuals in a manner akin to that of measles morbillivirus, which persists to cause annual outbreaks only when human communities exceed 250,000 to 500,000 (16). The persistence of measles virus within demographically heterogeneous human populations, whereby different communities are affected in different years, may give rise to viral persistence in spatially discrete "patches," in which infection dies out sequentially rather than simultaneously (17).

A different pattern of social structure is present among other colonial bats that have a metapopulation structure (consisting of periodically interacting, spatially discrete subpopulations). Flying foxes (*Pteropus* spp.) have such a structure. In this situation, the total number of individuals in the various subpopu-

lations or “patches” must be sufficient to maintain virus circulation in the metapopulation over time, while immunity or death due to viral infection extinguishes transmission chains within individual subpopulations. Periodic outbreaks of viral infection and disease may then be expected among given subpopulations in a region, once the number of susceptible individuals has recovered through births or loss of immunity, such that the populations once again can support viral transmission with an  $R_0$  of  $>1$ . Such periodic outbreaks of acute, even fatal viral disease are well documented for rabies virus among terrestrial carnivores (28) and may occur among vampire bats, as exemplified by the so-called “migration” of rabies virus in vampire bat populations in different regions with a 2- to 3-year cycle (19, 126). Preliminary modeling suggests that Hendra virus persists in Australian flying foxes in this way (H. E. Field, unpublished data).

Given that the phylogenetic distance of Hendra virus (and Nipah virus) from other viruses in the family *Paramyxoviridae* suggests that these are ancient viruses that likely have an evolutionary association with their flying fox hosts, it is both intuitive and biologically plausible that the maintenance of Hendra virus infection in flying foxes is based on the spatially heterogeneous population structure and nomadic nature of flying foxes.

### Echolocation

Microchiropteran bats are, with rare exceptions among the Megachiroptera (69, 71), the only land mammals that emit sounds and then detect and characterize the time delay and signal properties of returning echoes for the purpose of navigation (echolocation). Although certain birds and several species of megachiropterans use primitive echolocation, the degree to which neural and muscular systems of bats have evolved to produce echolocation signals, protect the individual bat from its own potentially deafening emissions, and decipher the information contained in returning echoes is unique. However, acoustic imaging is energy-intensive, corresponding to an energy flux of as much as  $6 \times 10^{-6}$  J/m<sup>2</sup> per echolocation call (113). The intense, high-frequency echolocation signals, ranging between 80 and 110 dB at a distance of 1 m from the emitting bat, approximate the range between the noise level produced by a coffee grinder and that produced at a rock concert or by a jet plane at ramp (5, 113). Echolocation signals are produced by the larynx, are powered by the muscles of the abdominal wall of bats, and are emitted through the mouth or nostrils (113). Production of such loud sounds also could generate droplets or small-particle aerosols of oropharyngeal fluids, mucus, or saliva, enabling transmission of viruses between individuals in close proximity. The hypothesis that rabies virus could be expelled from the nostrils of echolocating bats was supported by the isolation of rabies virus from mucus obtained from naturally infected Mexican free-tailed bats (39).

### Bat Immunology

Why can certain viruses infect and persist in apparently healthy bats yet be highly pathogenic for humans and other vertebrates? Because bats were among the earliest mammalian species to develop, it is possible that their innate and acquired

immune responses have important qualitative or quantitative differences from those of the rodents and primates which have been studied extensively. Do bats have a different set point in their immune responses, one that results in control of the level of virus replication without clearance of infectious virus in order to prevent immunopathological responses in infected tissues? Are all of the innate immune mechanisms that are presumed to have preceded the development of acquired immune responses also functional in bats? Is there affinity maturation of antibodies in bats? What are the properties of cell-mediated immune responses in bats? Significant differences in immune responses to viral infection likely will be found among the very large number and diversity of bat species, and it is unlikely that immunological reagents will be reactive across all bat species.

Very little is known about bat immune systems, although several studies suggest that immune responses of bats have some similarities with those of mammals that evolved after bats. For example, immunoglobulin G (IgG), IgA, and IgM have been purified from sera of great fruit-eating bats (*Artibeus lituratus*) (96). Macrophages, B- and T-lymphocyte-like cells, and cells expressing surface Ig were identified in the bone marrow of Indian flying foxes (*Pteropus giganteus*), indicating that lymphoid development is generally similar in bats and other mammals (26, 131). Presumably in bats, as with other mammals, the generation of high-titer IgG requires two events mediated by helper T cells: class switching and affinity maturation.

Serological assays that detect IgG antibodies to Hendra virus, severe acute respiratory syndrome coronavirus (SARS-CoV)-like viruses, and Ebola viruses in bats (66, 84, 85) indicate that some virus-specific adaptive T- and B-cell responses occur despite persistent virus infection. Further studies will require development of cell culture-based assays for examining lymphocyte proliferation, antibody synthesis, cytokine synthesis, and a host of other immunologic functions in bats.

### VIRUSES FOUND IN BATS

Table 2 lists the large number of viruses that have been isolated from or detected in bats, but most of these viruses have not been shown to be transmitted from bats to other animals or to cause human disease. Transmission from bats of viruses causing highly pathogenic disease has been demonstrated for rabies virus and related lyssaviruses, Nipah and Hendra viruses, and inferred for SARS-CoV-like virus of bats. The relationships of these viruses to their bat hosts and to zoonotic human diseases is described below. Other viruses in Table 2, such as certain alphaviruses, flaviviruses, and bunyaviruses, may infect bats via arthropods, but it is not clear whether bats are important reservoir hosts for these viruses. Clearly, a great deal of additional research is needed to document the roles of bats of different species in the natural history of the many viruses for which these remarkable animals can serve as hosts.

### Rabies Virus

It would be impossible here to summarize the scientific literature with regard to rabies and rabies virus. Therefore, we

will merely summarize what we believe is relevant to this review. Descriptions of a disease consistent with rabies date from 4,000 years ago. The Eshnunna code invoked penalties for knowingly allowing a “mad” dog to bite a human (12). In the first century of this era, Celsus warned of fatal bites from animals and suggested that such bites may contain venom (i.e., “virus”). However, it was not until the late 19th century that rabies virus was studied methodically. Louis Pasteur amplified the virus in rabbit spinal cord and prepared and administered a vaccine for postexposure prophylaxis. Those classical studies laid the foundations for virology and immunology.

Rabies virus (family *Rhabdoviridae*, genus *Lyssavirus*, serotype 1/genotype 1) is transmitted between mammals, including bats, primarily through the bite inoculation of rabies virus present in the saliva of infected individuals (95). The dual characters of transmitting rabies virus and being hematophagous (i.e., vampire bats) have cast a shadow on bats. Bats of three species (*Diphylla ecaudata* [hairy-legged vampire bat], *Diaemus youngi* [white-winged vampire bat], and *Desmodus rotundus* [vampire bat]) are known vampires and have been found to be involved in transmission of rabies virus, although available evidence indicates that only the latter is important in this regard (149).

Globally, a vanishingly small proportion of the approximately 55,000 annual human deaths caused by rabies virus are caused by variants of virus associated with bats (81). Although most cases of indigenously acquired human rabies in the United States are caused by bat-associated variants of rabies virus, the average of 1 or 2 cases per year over the past 2 decades indicates the rarity of these events (101). In the United States, most rabies victims do not recall having been bitten by a bat, which may be due to the small size of the biting animal or to unusual circumstances leading to the bite (127).

Recent evidence suggests that all rabies virus variants that affect terrestrial carnivores originated from cross-species transmission of bat-associated variants of rabies virus (10). A molecular clock model based on genetic divergence of rabies virus variants in bats of different species suggests that in North America the divergence of extant bat-associated rabies viruses from a common ancestor occurred about 1651 to 1660 C.E. The bat rabies virus variants found in Latin America in common vampire bats (*Desmodus rotundus*) and in free-tailed bats (genus *Tadarida*, family Molossididae) are closest to the earliest common ancestor. Adaptation of rabies virus variants occurred earlier and more rapidly in bats of colonial genera (genera *Eptesicus* and *Myotis*) than in bats of more solitary genera (*Lasiorycteris*, *Pipistrellus*, and *Lasiurus*) (74).

Bat variants of rabies virus sporadically spill over to infect mammals other than humans (97). Sustained transmission of bat variants of rabies virus within populations of red foxes on Prince Edward Island and striped skunks in Arizona (40, 45) proceeded until natural extinction or control by vaccination.

#### Lyssaviruses Related to Rabies Virus

Rabies virus is related to other lyssaviruses from bats, rodents, and arthropods (137). There are seven lyssavirus genotypes and an additional four novel genotypes recently recovered from bats in Eurasia (Table 2), which probably will be included in this genus (67, 151). Some of these viruses, most

notably Australian bat lyssavirus (ABLV) (140), can cause a fatal human illness indistinguishable from classic rabies (68, 129), but other lyssaviruses are not known to cause disease in vertebrates. The diagnosis of rabies in humans and animals traditionally was restricted to the acute fatal encephalomyelitis caused by rabies virus serotype 1/genotype 1, but now the disease “rabies” includes any of the fatal illnesses caused by any lyssavirus (67).

Details of the maintenance cycles for lyssaviruses other than rabies virus, such as Duvenhage, Lagos bat, and Mokola viruses (Table 2), are unclear (111). However, as with rabies virus, their perpetuation is assumed to involve bite transmission, primarily involving conspecifics of the reservoir host species, with occasional spillover to other susceptible vertebrates. Individuals of other species have been sporadically found to be infected by these rarely identified lyssaviruses, including a human with Duvenhage virus (100, 144), domestic cats and a dog with Lagos bat virus (54, 80, 98), and humans, domestic cats, and dogs with Mokola virus (15, 46, 47, 53, 110).

In May 1996, a lyssavirus was isolated from tissues of a black flying fox (*Pteropus alecto*) with signs of encephalitis found near Ballina, New South Wales, Australia (55). Six months later, a bat handler from Rockhampton, Queensland, Australia, developed numbness and weakness in her arm and later died from encephalitis. She had been infected with what is now known as ABLV. In 1998, a woman from Mackay (Queensland, Australia) was diagnosed with ABLV infection at her death, 2 years after having been bitten by a sick bat (68). Protection trials with mice conducted at the U.S. Centers for Disease Control and Prevention, Atlanta, Ga., indicated that a rabies human diploid cell vaccine might be useful for prophylaxis against this virus (90). Recent serologic evidence suggests that this virus also is present in bats in Thailand (88). 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 outbreak of an acute respiratory illness occurred in a human and 14 horses in Hendra, a suburb of Brisbane, Australia. Twenty-one horses and two humans (the trainer and a stable hand) were infected (109). Four additional outbreaks, in 1994, 1999, and 2004, infected five horses and two humans, killing all but one human (49, 72, 116, 123, 133).

A virus (family *Paramyxoviridae*, genus *Henipavirus* [named after Hendra and Nipah viruses]) was shown to be the etiologic agent of this disease (109). The natural hosts and probable reservoirs of Hendra virus are fruit bats (“flying foxes”) of the genus *Pteropus*, including the black flying fox (*Pteropus alecto*), gray-headed flying fox (*P. poliocephalus*), little red flying fox (*P. scapulatus*), and spectacled flying fox (*P. conspicillatus*) (50). Little is known about the dynamics of infection in flying foxes and how Hendra virus infection is maintained in them.

Field (50) proposed three alternative models for the maintenance of infection: (i) infection is enzootic in all species throughout their distribution; (ii) infection is enzootic in a particular species with a periodic epizootic pattern in the other species; or (iii) infection is periodically epizootic in all these species, persisting in a spatial or temporal mosaic across their distribution. He contends that the apparent pattern of known

“spillovers” from flying foxes to horses fits better with either of the two latter hypotheses. That is, a periodic outbreak in a local population of flying foxes results in an increased probability of spillover to horses in a specific locality during a limited time period. An outbreak of Hendra virus infection in a local population of flying foxes may depend on attainment of a threshold number of susceptible flying foxes in the population and introduction of the virus into the population from a nomadic individual or group. These concepts are well studied for related morbilliviruses (17, 146). A situation analogous to the circumstances being proposed for spillover of Hendra virus to horses has been described for rabies virus spillover to domestic cats. In the eastern United States, there is a strong association between the local temporal dynamics of rabies epizootics within a reservoir host species, in this case the raccoon (*Procyon lotor*), which serves as the regional reservoir host for a specific variant of rabies virus, and an increase in the risk of rabies spillover to domestic cats (59).

Nipah virus, a paramyxovirus related to Hendra virus, was first isolated in 1999 from pigs and adult human males affected by fever and encephalitis, some with respiratory illness, during a major outbreak in peninsular Malaysia and then in Singapore (23, 24, 31). Of 265 reported human cases, 105 were fatal. Direct contact with infected pigs was identified as the predominant mode of human infection (33, 57). Most of the humans affected in the Malaysian outbreak had a history of direct contact with live pigs, and most were adult male Chinese pig farmers (31, 117). More than 1 million pigs were culled to contain the outbreak. With the knowledge that *Pteropus* species bats were the likely reservoir of the closely related Hendra virus in Australia, Malaysian bats were prioritized for surveillance. Like most other countries in Southeast Asia, Malaysia has a great diversity of bat species, including 13 species of Megachiroptera and 60 species of Microchiroptera (99). The large flying fox (*Pteropus vampyrus*) and the variable flying fox (*P. hypomelanus*) were found to be natural reservoir hosts for Nipah virus (34, 76).

Since 2001, sporadic outbreaks of Nipah virus-associated disease in humans have been identified in Bangladesh (6, 7, 8, 73). Although many characteristics of these outbreaks were similar to those of the Malaysian outbreak, including delayed recognition, a primary presentation with fever and central nervous system signs, and a high case fatality rate, in Bangladesh the human cases were not associated with disease in pigs, and there was some evidence suggesting human-to-human transmission (73). Serologic surveys of domestic and wild animals undertaken after the 2001 and 2003 outbreaks in Bangladesh provided evidence of Nipah virus infection only in Indian flying foxes (6, 73). Concurrent 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. Chadha et al. (25) recently reported the occurrence of Nipah virus infections in humans in India in 2001. Neutralizing antibodies to Nipah virus were found in large flying foxes in Indonesia (134) and Cambodia (114), and Nipah virus was isolated from Lyle's flying fox (*Pteropus lylei*) in Cambodia (121). Thus, the henipaviruses likely occur across the entire global distribution of pterid bats (66).

Available evidence suggests that Hendra and Nipah viruses are ancient viruses that have long circulated in their natural hosts, flying foxes (60). What precipitated the apparent recent emergence of these viruses? Can we identify environmental factors that altered flying fox ecology and facilitated the movement of henipaviruses (and other bat-associated zoonotic agents) beyond their natural ecological niches? Disease emergence requires, in addition to the presence of an agent, an effective bridge from the natural host to a susceptible spillover host. Such bridges may be caused by changes to the agent, the host, or the environment. Data on fruit bats of many species suggest that populations are in decline throughout their range, primarily as a result of habitat loss and hunting. In Australia, fruit bat roosting sites recently have been increasingly redistributed to urban areas (64). A scenario emerges of flying fox populations under stress, altered foraging and behavioral patterns, and virus niche expansion, all leading to closer proximity to humans and livestock. This certainly was the case with Nipah virus emergence (35). Chong et al. (30) suggested that the risk of humans contracting Nipah virus infection from bats is low. Once Nipah virus escapes its natural cycle, its epidemiologic characteristics are quite a different story.

#### Menangle and Tioman Viruses

Menangle virus (family *Paramyxoviridae*, genus *Rubulavirus*) was isolated in 1997 from stillborn piglets at a large commercial piggery near Menangle in Australia (118); the bat colony and the piggery had coexisted for 29 years before the incident. There were large numbers of within-litter fetal deaths at a variety of gestational ages. Most sows carried their litters to term, but abortions occasionally occurred. Affected litters included mummified, autolyzing, fresh stillborn, and live piglets. Teratogenic defects frequently seen included arthrogryposis, brachygnathia, and kyphosis. Internally, part or all of the brain and spinal cord was absent in most piglets, and there was malacia and nonsuppurative inflammation of the brains and spinal cords of some. Nonsuppurative myocarditis and hepatitis also were present in some piglets (118).

Two of 250 humans in contact with the infected pigs had high titers of antibodies to the new virus, and both reported a febrile illness with a measles-like rash, but neither had direct exposure to flying foxes (27). Individual bats living in a large, mixed colony of gray-headed flying foxes and little red flying foxes seasonally, and roosting within 200 m of the affected piggery, had neutralizing antibodies (118), as did flying foxes of other species from other colonies thousands of kilometers distant and previous to the outbreak at Menangle (Field, unpublished); other species in the vicinity of the affected piggery were seronegative. Although attempts to isolate virus from flying foxes were unsuccessful, 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 (32).

### SARS-CoV-Like Viruses of Bats

In 2002, a previously unrecognized coronavirus (family *Coronaviridae*) was found to cause a new, severe acute respiratory syndrome in humans (92, 125). This virus, named 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 (58). It is distinct from two other coronaviruses recently identified in bats in southern China (84, 119).

Epidemiologic studies showed that the earliest cases of SARS were associated with the wildlife meat industry. A survey of wildlife in a Shenzhen market recovered SARS-CoV-like viruses from masked palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*) and detected antibodies to the SARS-CoV-like virus in a hog badger (*Arctonyx collaris*) (63). Interestingly, the epidemiology of the outbreak in animals in the wildlife meat market resembled that of shipping fever, a viral syndrome that occurs when animals from different farms are comingled under crowded, stressful conditions. Under such circumstances, immune responses to persistent virus infections are reduced, virus shedding is increased, and susceptible animals become infected and shed virus. In the marketplace where SARS-CoVs were detected, viral RNA from some animals that were seronegative was detected by reverse transcription-PCR, suggesting acute infection, while other animals had antibodies to SARS-CoV but continued to shed virus, suggesting persistent infections (63). Although no pathology was associated with SARS-CoV in animals in this market, civets inoculated with human isolates of SARS-CoV had severe lung pathology (156). By sequencing many viral genomes from SARS patients, wild and farmed civets, and other animals, a dendrogram was generated that showed that the first human SARS coronaviruses were closely related to a contemporary virus from masked palm civets and that point mutations were selected and accumulated later, as the virus passed from human to human (139).

Extensive surveys of viruses in domestic animals, poultry, and wildlife were done by reverse transcription-PCR to identify the natural reservoir of SARS-CoV. Palm civets were found to be an incidental host rather than the principal host for SARS-CoV. Recently, several groups simultaneously identified bats from different locations in southern China as being infected with SARS-CoV-like viruses or having antibody to these newly recognized coronaviruses, including members of several species of Chinese horseshoe bats (suborder Microchiroptera, family Rhinolophidae, genus *Rhinolophus*) (Tables 1 and 2) (42, 84, 86). The prevalence of antibody to bat SARS-CoV in some species of Chinese horseshoe bats was as high as 84%. Pathology has not yet been associated with SARS-CoV infection of bats.

The genomes of SARS-CoV isolates recovered from civets and humans during the 2002-to-2003 outbreak of SARS lay phylogenetically within the broad group of SARS-CoV-like viruses of bats (86). These data show that the virus responsible for the 2002-to-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 cave-dwelling 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 (139).

### Ebola Viruses

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*; Marburg virus comprises the genus *Marburgvirus*. The natural reservoir hosts of these viruses have not yet been identified. However, Ebola virus RNA has been detected in terrestrial mammals in the Central African Republic (107). Experimental infections of the Angola free-tailed bat (*Mops condylurus*), little free-tailed bat (*Chaerephon pumilus*), and Wahlberg's epauletted fruit bat (*Epomophorus wahlbergi*) with Ebola Zaire virus led to replication of virus in these bats (145). Recently, Ebola virus RNA was detected in liver and spleen tissues of three fruit bats: the hammer-headed fruit bat (*Hypsignathus monstrosus*), Franquet's epauletted bat (*Epomops franqueti*), and little collared fruit bat (*Myonycteris torquata*) (85). Ebola virus-specific immunoglobulin M antibody was detected in bats of the same species, but Ebola virus RNA was not detected in bats with antibody, and antibody was not detected in bats with Ebola virus RNA.

Detection of Ebola virus RNA in bats and rodents is a fascinating finding, as is detection of antibody. However, until and unless an Ebola virus (or Marburg virus) is isolated from a wild vertebrate, and experimental infections unambiguously demonstrate that the virus not only persists but is shed by that animal and that disease can be transmitted under controlled conditions, these findings will remain simply intriguing and promising. Monath has postulated that there may be an as-yet-undetected Ebola virus, one that is nonpathogenic but may give rise to pathogenic genotypes by mutation, and that the filoviruses may be arthropod or plant viruses (105).

### IMPLICATIONS FOR FUTURE RESEARCH ON EMERGING VIRUSES OF BATS AND OTHER WILDLIFE

#### Emerging Viruses and Wildlife Surveillance

Scores of newly recognized viruses have emerged in recent decades, and elegant reviews have brought into focus the continuing importance of this phenomenon (91). It seems surprising, as though we are caught unawares, when a hitherto unrecognized disease and its causative virus are discovered. Recognition of the spillover of a zoonotic virus is precipitated by human, livestock, or wildlife deaths, with considerable medical, emotional, and economic miseries. 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. When new emerging zoonotic viral diseases appear, reviews and grant applications are written, explanations proffered, symposia or-

ganized, and molecular and other specific diagnostic tools developed. Unfortunately, one important method to predict emergence of zoonotic diseases that has been overlooked repeatedly is the natural history survey, followed by targeted studies of species of interest identified through the survey. Survey research followed by targeted study has been used successfully to explore the epidemiology of reservoir host-zoonotic virus maintenance, as exemplified by studies on hantaviruses in the southwestern United States (102, 103). These studies 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 (22, 51, 52, 56).

From about 1930 to about 1970, governments and private institutions emphasized sending people into the field to count, trap, measure, bleed, and test vertebrates and invertebrates for viruses. Although those surveys may not have provided answers directly and quickly, they did provide specimens for future analyses and questions to be addressed. Many "orphan" viruses without known connection to disease were discovered. Information regarding more than 500 viruses was collected by the American Committee on Arthropod-Borne Viruses and published in the *International Catalogue of Arboviruses Including Certain Other Viruses* (78). This invaluable but badly outdated compendium is slowly being replaced by Internet resources as a means of information dissemination. Supplementing and replacing this printed catalogue are numerous databases (e.g., ICTVdB, The Universal Virus Database of the International Committee on Taxonomy of Viruses, available at <http://www.ncbi.nlm.nih.gov/ICTVdb/>). Nevertheless, most of the current data are limited in scope and in imagination. What is needed is a survey of viruses of all vertebrates, invertebrates, plants, and other life forms. Although thoughts of complete surveys obviously are wishful thinking, some survey efforts are better than none.

Information about the natural history of most viruses in bats is limited. Regarding the conservation status of 914 bat species listed by Wilson (153), omitting those that are, or are suspected to be, extinct, 390 (42.7%) are considered not assessed (adequately), 297 are considered stable, 201 are considered vulnerable or potentially vulnerable, and 26 are considered endangered. Of the 390 species that have not been assessed adequately, 38 (9.7%) are of the family Pteropodidae, the Old World fruit bats, from which the most recent virus emergences have been observed. These 38 represent 59.4% of the 64 genera in this family, indicating that we know relatively little about the bats from which zoonotic viruses that cause human disease have recently emerged. To various degrees, this can be said about all bats, if not about all vertebrates.

Obviously, there is a need for comprehensive surveys of bats in every place where they occur, although conservation concerns must be addressed in the design of survey and sampling methods, given that bats of many species are protected. Non-killing techniques involving bleeding or procuring of oropharyngeal and rectal swabs for PCR-based analyses, in addition to collection of recently dead individuals, have been used to determine viral infections and the prevalence of antibodies in bats (see, e.g., references 43, 114, and 115). We know very little about the 925 bat species that have been recognized, placed in a taxon, and largely ignored after that. How many unrecog-

nized viruses do those bats harbor? Will any or all of these viruses eventually be shown to be human, livestock, or wildlife pathogens? What new viruses lurk in the other nearly 4,000 species of mammals and the thousands of species of other vertebrates, invertebrates, plants, and individuals of other kingdoms, phyla, and classes? In effect, without even partial predictive capacity, we are simply waiting for the next disastrous zoonotic virus outbreak to occur. Clearly, this is not an effective prevention or prediction philosophy.

However, there is no simple solution to this need. Perhaps part of the problem is lack of interest (ignorance?), and part is due to lack of funding (there is not enough money for everything). Surely in some countries, principally those from which emerging disease are emerging, there is a lack of infrastructure, manpower, and even national will; these are political questions. We suggest holding international symposia emphasizing the importance of both natural history surveys and of knowledge as not only predictive tools but also disease-prevention tools. Further emphasis on greater prioritization of such studies might be shown to be very cost-effective in the long run.

### Virus Isolation and Characterization

Virus isolation techniques and PCR assays now are extremely sensitive and rapid. These methods could provide the opportunity to collect and store a massive amount of information to accompany bat sera and tissue specimens. This would provide us with at least some degree of intellectual preparedness and with reagents that could be used to develop rapid diagnostic assays for newly emerged viruses.

When a newly recognized virus is detected, virus identification is now done by PCR amplification of viral nucleic acid, and the resulting sequence data are compared with sequences in the genetic databases, such as GenBank (<http://www.ncbi.nlm.nih.gov/GenBank/>), to search for similarities with sequences of recognized viruses. In addition, viral proteins (antigens) can be expressed and used for serodiagnostic tests. If possible, the infectious virus is isolated, antigens are prepared for diagnosis, and experimental infections are conducted to study pathogenesis. Emerging viral diseases often are misdiagnosed. For example, when the Nipah virus infection was first reported in Malaysia in 1999, the diagnosis was "JEV infection," even though (i) all the human patients were adult males, (ii) most or all of those people had been vaccinated against JEV, (iii) pigs suffered fatal disease (pigs do not die when infected with JEV; they serve as amplifying hosts for that virus), and (iv) a virus isolated from patients with the disease appeared by electron microscopy to be a paramyxovirus, not a flavivirus, as JEV is. Only after it was realized that an intensive JEV vaccination campaign was not diminishing transmission of this new disease were other approaches initiated; by then, valuable time and many lives had been lost. That outbreak can serve as an example of our perpetual following of epidemic curves rather than predicting them, of our lack of early recognition of emerging diseases.

### Diagnostic Limitations

At this time, diagnostic reagents or tests are available for all the viruses shown in Table 2. However, to detect previously

unrecognized viruses, new reagents and approaches must be developed or existing techniques applied. Among the new reagents, a variety of nested primers useful for exploratory PCR might be formulated based on knowledge of sequences of recognized viruses within the order *Mononegavirales* (which includes *Bornaviridae*, *Rhabdoviridae*, *Filoviridae*, and *Paramyxoviridae* [120]). In addition, bat family-specific or genus-specific conjugates could be produced and applied for use in immunofluorescence assays or in enzyme-linked immunosorbent assays to identify antibodies in sera or blood samples, or antigens in tissue samples. Classical methods including hemagglutination-inhibition tests, which are broadly cross-reactive, also could be developed using inactivated antigens prepared from various recognized viruses. Virus isolation assays, while potentially quite hazardous, also can be applied if used with appropriate biocontainment. In this day of increasing emphasis on molecular genetic tools for detecting viral nucleic acids and for identifying nucleotide sequences rather than the viruses themselves, it is frequently overlooked that virus isolation provides us with a virus. With the virus itself, many areas of research and development can be addressed, including development of diagnostics, of animal disease models, and of vaccines. Emphasis, sometimes complete emphasis, on nucleotide sequence characterization rather than virus characterization has led us down a primrose path at the expense of having real viruses with which to work.

#### Studies on Immune Responses of Bats

To understand the innate and acquired immune responses of bats during acute and chronic virus infections, much additional research is needed. It will be necessary to develop bat cell culture-based assays and bat-specific reagents to examine lymphocyte proliferation, antibody and cytokine synthesis, cell-mediated immune responses, and a host of other immunologic functions in bats that are important reservoirs of emerging viruses. A major challenge in studying T-cell responses in bats is the apparent lack of inbred strains of bats. Such animals are needed for long-term T-cell studies because of the requirement for matched major histocompatibility complex molecules on T cells and antigen-presenting cells. Colonies of captive bats might carry zoonotic viruses that could be transmitted to humans, so research on the bats and their cells might require biological containment. In rodents, the growth factors required for *in vitro* expansion and maturation of bone marrow stem cells into competent antigen-presenting cells have been partially characterized, leading to development of cell culture assays for intermediate-term propagation of rodent T cells (41). Similar strategies likely can be employed for propagation of T cells from bats of various species.

Molecular genetics should be useful for analyzing bat immune responses. More than 4,000 protein-encoding sequences from chiropterans are in the National Center for Biotechnology Information databases (<http://www.ncbi.nlm.nih.gov/>), but of these only sequences for recombination activation genes 1 and 2 are immunologically relevant. Despite this limitation, it should be possible to develop assays for evaluating such responses in infected bats. Perhaps most tractable and meaningful for understanding these responses are analyses of cytokines and chemokines, especially in conjunction with cell culture assays. Capture enzyme-linked immunosorbent assays and flow

cytometry-based assays for a number of cytokines and chemokines from conventional species have permitted an elegant dissection of immune responses in humans and rodents. However, development of monoclonal antibody pairs for cytokine detection assays requires substantial funding and effort. More recent developments employing molecular approaches, such as real-time PCR, cDNA arrays, and RNase protection assays, have accelerated development assays for cytokine and chemokine gene expression. These assays will require sequencing of bat orthologs, but considering that 11 assemblies of mammalian genomes are already available, it is likely that most genes from bats of most species could be cloned and sequenced using degenerate PCR primer sets, a strategy that has been used for other species (132). Once the relevant gene sequences are known for bats of a given species, real-time PCR assays could be developed. In conjunction with cell culture studies, it should be possible to characterize bat immune responses to challenge with viral antigens. Bacterial artificial chromosome libraries are available for the little brown bat and the greater horseshoe bat, a species closely related to the Chinese horseshoe bat (*Rhinolophus sinicus*), a host for SARS-CoV-like virus (84; <http://bacpac.chori.org/libraries.php>). These resources may be particularly valuable for rapidly identifying immune response or cytokine genes of interest by using human or mouse hybridization probes.

#### Immune Evasion and Virus Persistence

Viruses must evade the host immune response for a time sufficient to allow transmission to other susceptible hosts or to establish persistent infection. The strategies employed by viruses are numerous and target both the innate and adaptive phases of the immune response. Some commonly employed evasion strategies include virus-encoded immune-modulating cytokines, decoy soluble cytokine receptors, inhibitors of apoptosis and cellular signaling, inhibitors of antigen processing, and T-cell antagonists (2, 3, 18, 61, 70, 79, 87, 104, 150, 152). To persist, viruses must also become biochemically adapted, so that they can replicate without severely compromising the host's survival.

Some viruses, including SARS-CoV, elicit an immune response in the nonreservoir host that may contribute to pathology (75, 148, 157) while apparently, at least for SARS viruses, not causing immunopathology in the reservoir. Elucidating the immune responses in reservoir hosts that determine the balance between virus persistence and immunopathology could contribute to our understanding of viral pathogenesis in humans and reveal potential targets for therapeutic intervention.

Some paramyxoviruses, including Nipah and Hendra viruses, encode V proteins that bind to signal transducer and activator of transcription 1 (STAT1) and STAT2 proteins of host cells to block both alpha/beta and gamma interferon responses (122). How the viral proteins might affect potential interferon responses to virus infections in bats is unknown. Possibly the V proteins play a role in viral persistence and evasion of the immune response. Addressing these important issues regarding the pathophysiology of viral infections in bats will require the development of infection models for reservoir species of each zoonotic virus.

With regard to bats, there is evidence that "healthy bats" can

be asymptotically infected with rabies virus. In nonlethal rabies infections produced in Mexican free-tailed bats, individuals surviving infection do not have virus in the brain or saliva. In one experimental study of free-tailed bats inoculated with salivary gland tissues from naturally infected bats, the incubation periods were 24 to 125 days, but one asymptomatic bat sacrificed at the end of the study had rabies virus in the brain, salivary glands, and other organs (11). Incubation periods for rabies virus are certainly highly variable in bats, and persistence of virus in hibernating bats has been suggested as serving a viral reservoir function (143). A carrier state for rabies virus has also been suggested by experimental and observational studies among dogs in Ethiopia (48).

### Discovery of Emerging Viruses in Wildlife

It is, perhaps, instructive that viruses of the families *Paramyxoviridae*, *Filoviridae*, *Bornaviridae*, and *Rhabdoviridae* are phylogenetically related and have been grouped in a single order, the *Mononegavirales* (120). There are at least 250 recognized viruses in this order, including some that infect humans, other primates, livestock, birds, dogs, seals, fish, crabs, mosquitoes, ticks, amoebae, plants, or bats. If there is an unrecognized tendency for bats and viruses to be associated, viruses of this order would be prime targets for beginning the search.

Essentially every living life form investigated has been shown to host viruses, and bats are no exception. However, it is reasonable to query the roles of viruses of bats. What role, for example, does a fruit-eating bat play in the life cycle of a human or livestock pathogen? If human and livestock infections from bats simply are host-switching phenomena, why have these viruses not been recognized previously, and why have they emerged now? Are these events the results of ecologic alterations, such as impingement of human activities on heretofore virgin areas, consequences of global climate change, or the product of improved surveillance activities coincident with the technical advances in diagnostic capabilities required to identify heretofore undescribed zoonotic viruses?

Are viruses of bats symbionts, parasites, or commensals? Is pathogenicity for humans and livestock simply a freak occurrence? Perhaps these emerging bat viruses are naturally transmitted by arthropods or by other potential vectors that have not been examined. Surely a fatal infection in a host is not in the long-term best interest of the virus. Might fruit-eating bats transmit viruses to or from plants? How? Are insectivorous bats intermediate hosts between insects and vertebrates (or plants)? Are fruiting events part of periodic amplification cycles of viruses from frugivorous bats to wildlife and humans, as suggested by Dobson (42)? Childs summarized the processes by which zoonotic viruses are transmitted (29). He noted the rarity of surveillance for wildlife diseases or infections and suggested that such studies usually are outbreak-driven, i.e., after an epidemic of a newly recognized virus has emerged.

Outbreaks of Hendra virus, Nipah virus, Menangle virus, SARS-CoV-like viruses of bats, and European bat lyssavirus 1 (108) have not been recognized more than once or a few times. Are transmissions between bats and other vertebrates infrequent, incidental spillover events? Do many of the 66 viruses listed in Table 2 represent fortuitous, irrelevant events, or have

we detected only the tip of the iceberg? Do bats differ from other mammals in their ability to clear viral infections? Does the persistence of asymptomatic viral infections in bats indicate that bats are an important reservoir for the wide variety of viruses in nature? Is the prevalence of RNA viruses in persistent infections in bats indicative of a defect in host resistance or viral clearance mechanisms, such as interferon or interferon-responsive genes that lead to clearance of RNA viruses from other vertebrates? There is some urgency to explore these important questions.

There is no reason to believe that bats are different from other mammals with regard to species specificity of host susceptibility to virus diseases, nonuniform persistence of viral infections, or mechanisms of virus shedding, so that such investigations likely do not require development of new assay systems or diagnostic concepts. Additional research is needed to determine the roles played by bats of various species in the natural histories of the viruses for which bats can serve as hosts.

One or more of the 66 viruses listed in Table 2 have been isolated from bats of 74 species. As well, viruses have been isolated from bats not identified further than to genus level and from four unidentified bats. Some viruses have been isolated from bats of as few as 1 species and one from as many as 14. Clearly, bat handlers, people entering bat habitat areas, and people who usually think in noninfectious disease terms regarding various studies of the bats themselves should take necessary precautions to avoid exposing themselves to recognized and unrecognized viruses and to other human pathogens which the bats may harbor.

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### ADDENDUM IN PROOF

In addition to finding a recent publication reporting the identification of six novel coronaviruses from six different bat species in Hong Kong alone (P. C. Woo, S. K. Lau, K. S. Li, R. W. Poon, B. H. Wong, H. W. Tsoi, B. C. Yip, Y. Huang, K. H. Chan, and K. Y. Yuen, *Virology*, Epub ahead of print, doi:10.1016/j.virol.2006.02.041, 2006), we have learned of other viruses isolated from or detected in bats from Africa and of many as-yet-unpublished viruses recently detected in bats in

Australia. Thus, our article may contain only an indication of the great potential for future discoveries of viruses in bats worldwide.

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