

Bats, emerging infectious diseases, and the rabies paradigm revisited

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The significance of bats as sources of emerging infectious diseases has been increasingly appreciated, and new data have been accumulated rapidly during recent years. For some emerging pathogens the bat origin has been confirmed (such as lyssaviruses, henipaviruses, coronaviruses), for other it has been suggested (filoviruses). Several recently identified viruses remain to be 'orphan' but have a potential for further emergence (such as Tioman, Menangle, and Pulau viruses). In the present review we summarize information on major bat-associated emerging infections and discuss specific characteristics of bats as carriers of pathogens (from evolutionary, ecological, and immunological positions). We also discuss drivers and forces of an infectious disease emergence and describe various existing and potential approaches for control and prevention of such infections at individual, populational, and societal levels.

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Infectious diseases continue to emerge and the majority of these are zoonotic in origin (1, 2). Zoonotic infections, particularly those caused by RNA viruses, have been recognized as a significant human health threat, particularly in developing countries (3). The significance of bats as reservoirs of such emerging infectious diseases (EIDs) has been increasingly appreciated (4). New pathogens are documented in bats every year and most of these new agents still require characterization. The majority of studies performed to date have focused on infections of significant public health and veterinary concern. In this paper, we summarize the available information on several selected pathogens, including lyssaviruses, coronaviruses, henipaviruses, and filoviruses, for which a considerable amount of information has been collected to date on a global basis (Fig. 1).

Bat rabies—a global threat

Rabies is an acute progressive encephalitis caused by viruses in the Genus *Lyssavirus*, Family *Rhabdoviridae*, with the highest fatality rate among conventional infectious diseases. Known in bats for well over a century, rabies is the best studied infection associated with the Chiroptera. Bats are the principal reservoirs for 10 of the

11 recognized lyssavirus species and are suspected as hosts of other putative species (5). Only one lyssavirus, Mokola virus (MOKV), has never been isolated from bats to date. However, the principal reservoir for MOKV is unknown (6). Another viral species, rabies virus (RABV), circulates in bats and other mammals (predominantly carnivores). Interestingly, RABV circulates in bats only in the Americas, whereas in carnivores, the disease circulates globally. In the Old World, bats maintain circulation of other lyssavirus species, such as Lagos bat virus (LBV), Duvenhage virus (DUVV), European bat lyssaviruses type 1 (EBLV-1) and 2 (EBLV-2), Australian bat lyssavirus (ABLV), Aravan virus (ARAV), Khujand virus (KHUV), Irkut virus (IRKV), West Caucasian bat virus (WCBV), and Shimoni bat virus (SHIBV). For these viruses, bats are the principal hosts, with only a few spillover infections documented in other mammals. Isolation of RABV from Eurasian bats has been suggested several times, but never confirmed (reviewed in Kuzmin and Rupprecht (7)). Indeed, the surveillance data from developing countries is very limited. We do not know which lyssaviruses circulate in bats of northern Africa and southern Asia, although historical reports (8, 9) along with more recent serological findings (10–12)



Fig. 1. Bat-associated and presumable bat-associated EIDs. Abbreviations: RABV, =rabies virus; EBLV-1,2 =European bat lyssaviruses type 1 and 2; WCBV =West Caucasian bat virus; ARAV =Aravan virus; KHUV =Khujand virus; IRKV =Irkut virus; LBV =Lagos bat virus; SHIBV =Shimoni bat virus; DUVV =Duvnaha virus; MARV =Marburg virus; EBOV =Ebola virus; Filovirus =unclassified filovirus detected in bats in Europe; HeV =Hendra virus; NiV =Nipah virus; Henipavirus =unclassified henipavirus; SARS-CoV =SARS coronavirus.

indicate that bats do maintain lyssavirus circulation in these territories.

A paralytic disease in cattle and sporadically in humans bitten by a vampire bat has been reported from the time of the Spanish first colonized Latin America. However, the diagnosis of rabies was first confirmed by the identification of Negri bodies in the brain of cattle during an outbreak in Brazil in 1911 (13). Vampire bats probably maintained rabies virus circulation for a long time prior to the arrival of Europeans in the Americas. The association between vampire bites and the disease was understood by natives, who cauterized or washed the bites to prevent the disease (14). However, historical antecedents might be some other progenitor virus, quite different from those ones that circulate in bat populations presently.

Economic losses due to vampire bat rabies in livestock are tremendous. In the enzootic area there is an at-risk population of more than 70 million head of cattle. Vampire bats usually bite many animals in a herd. The proportion of animals bitten may vary from 6 to 52% (15). Significant outbreaks of vampire bat rabies were documented in Amazon area (Brazil, Peru) during recent years. Up to 23–55% of respondents interviewed had vampire bat bites during the last year. During the outbreaks, up to 15% of such bites caused rabies in humans (reviewed in Kuzmin and Rupprecht (7)).

An idea that vampire bats may be asymptomatic rabies carriers, shedding the virus in their saliva for months, was popular during initial studies of vampire bat rabies (16). However, in a well-documented experimental study by Moreno and Baer (17), the disease in vampire bats was similar to rabies observed in other mammals. The bats

that developed signs of disease and excreted the virus via saliva soon died, whereas those that survived the inoculation without clinical signs never excreted the virus or had it in the brain as demonstrated upon euthanasia. More recently, the asymptomatic excretion of RABV in the saliva of experimentally infected vampire bats, which survived the challenge during at least 2 years of observation, was documented again (18). Clearly, this phenomenon requires additional investigation.

Rabies of insectivorous bats was first documented in 1953 in Florida. Later it was documented across the United States, in Canada, and Latin America. Several RABV lineages were documented, and in general, they correspond to particular host species (reviewed in Kuzmin and Rupprecht (7)). Moreover, widely distributed bat species, such as Mexican free-tailed bat (*Tadarida brasiliensis*) and big brown bat (*Eptesicus fuscus*), maintain circulation of several RABV variants across their geographic range. Insectivorous bats are the major source of human rabies in the United States and Canada, which became especially prominent after elimination of RABV circulation among dogs. During 1958–2009, a total of 49 naturally acquired human rabies cases caused by bat RABV variants were reported in the United States and Canada (excluding four rabies cases caused by organ transplantation from a donor who died of unrecognized rabies) (19,20). In 19 of these cases the exposure was ‘cryptic’, as the patients did not recall any contact with animals or a bat was seen flying in the residence but no direct physical contact was reported. Appears that some bat bites, especially if they were inflicted by small bat species, may be ignored or not recognized as dangerous

by people (such as a previously unattended child, mentally disabled, or intoxicated person).

Two closely related RABV variants (previously considered as one), associated with the silver-haired bat (*Lasionycteris noctivagans*) and eastern tri-colored bat (*Perimyotis subflavus*) have caused about 60% of human rabies cases, where the virus variant could be identified. These bats are relatively small, do not form large colonies, and usually do not roost in close proximity to human dwellings. In contrast, the big brown bat RABV variant and the *Myotis* RABV variant caused one human case each, even if these bats frequently occupy house attics and crevices in men-made constructions. Furthermore, big brown bats constitute about 90% of all rabid bats, submitted to diagnostic laboratories in the United States and definitely have more contacts with humans (21,22). The Mexican free-tailed bat RABV variant caused several human rabies cases as well, including four cases that occurred in 2004 after transplantation of organs and vessel from a donor who died of rabies (23). Several versions were suggested to explain the disproportional prevalence of the silver-haired bat and eastern tri-colored bat RABV variant among human rabies cases. Investigations suggested that these viruses have enhanced pathogenicity to humans, for example they may have a greater ability to replicate in fibroblasts and epithelial cells, being delivered into a superficial bat bite (24).

In the Old World, the significance of bat rabies for veterinary and public health is well addressed only in the countries with developed surveillance systems, such as Western Europe and Australia. The EBLV-1 and EBLV-2 circulate in Europe among insectivorous bats *Eptesicus fuscus* and *Myotis* spp, respectively. These viruses caused at least three cases of human rabies, where the virus was characterized, in Finland, Russia, and in the UK (reviewed in Kuzmin and Rupprecht (7)). The IRKV, first identified in insectivorous bat *Murina leucogaster* in eastern Siberia during 2002 (25), was known by this only one isolate until 2007, when it caused a human death after a bite of unidentified insectivorous bat in the Russian Far East (26). Moreover, at least three other cases, where the viruses were not identified but the disease was compatible with rabies and developed after bat exposure, were reported from the Ukraine and China (27–29). A few cases of spillover EBLV-1 infections were documented in terrestrial mammals, including domestic cats (30), and they represent a potential exposure risk for humans.

The EBLVs, as well as IRKV, are covered by the commercially available rabies biologics (31,32), therefore the disease can be efficiently prevented by administration of standard rabies post-exposure prophylaxis (PEP). This is not the case for WCBV. This virus, isolated from insectivorous bat *Miniopterus schreibersii* in south-eastern Europe, is the most divergent member of the *Lyssavirus*

genus, and rabies biologics are incapable of providing significant protection against it (32). Because of lacking surveillance, there is only one isolate of WCBV available to date. Ecology of this virus and its significance for public health are unknown. However, laboratory animals and bats, infected with WCBV, developed typical rabies and died (33).

A variety of bat lyssaviruses have been documented in Africa. The LBV, first documented in Nigeria in 1956 (34), was further isolated in many sub-Saharan countries (35). Moreover, in 1999 it was imported into France with fruit bats *Rousettus aegyptiacus* captured in Togo or Egypt (36). Fruit bats of several species serve as reservoir hosts for LBV, with infrequent spillover infections documented in dogs, cats, and a mongoose (37). The viruses, currently included into LBV, represent several divergent lineages and there is a possibility that further taxonomic efforts may facilitate separation of these viruses into two or three species (5,38,39). Another divergent lyssavirus, SHIBV, was isolated from insectivorous bat *Hipposideros commersoni* in Kenya in 2009. The SHIBV demonstrates similarity to MOKV and LBV, but cannot be included into any of these species (5). Significance of these viruses for public health is unknown however, as in the case of WCBV, they are pathogenic for laboratory animals, which develop rabies and die after intracranial or peripheral inoculation (5,35,40). Furthermore, due to their antigenic differences, they are not covered by current rabies biologics (32,41).

Recently, serologic reactivity to WCBV was detected in *Miniopterus* bats of several species from Kenya (42). Given that WCBV does not cross-react serologically with other known lyssaviruses, this seroprevalence indicates that WCBV or some other antigenically similar virus circulates in Africa as well (and probably more broadly, corresponding to the distribution range of *Miniopterus* bats).

Another African bat lyssavirus, DUVV, is covered by rabies biologics, but still kills people because of insufficient knowledge, either in general public and health professionals. The DUVV is perhaps the most mysterious African lyssavirus. Of four isolates available, three came from humans who died of rabies after bat exposures and only one was isolated from an insectivorous bat, presumptive *Miniopterus* sp (43). The most recent human case occurred in 2007 in Kenya, where a Dutch tourist was attacked by a bat in a campsite of Tsavo West national park. The patient applied for medical help, but a local physician assured that bat rabies does not exist in Kenya and PEP was not administered. Several weeks later, back in the Netherlands, the patient developed rabies and died. The virus was identified as DUVV (44).

The discovery of ABLV in 1996 in the 'rabies-free' Australia was surprising. Following the discovery that flying foxes were a reservoir of Hendra virus, surveillance

of these animals was increased. During this activity, ABLV was identified first in a sick black flying fox (*Pteropus alecto*). The second case was diagnosed retrospectively in another bat of the same species, sampled in 1995 with signs of unusual aggressiveness (45). Later ABLV was documented in each of the four flying fox species, present in continental Australia. Furthermore, a genetically divergent variant of ABLV was discovered in insectivorous bats *Saccolaimus flaviventris* (46).

Two human cases of ABLV infection have been documented to date. Both were fatal and clinical symptoms were compatible with rabies. The first one was reported very shortly after the virus discovery in 1996. The patient was a 39-year-old female presumably infected by a *S. flaviventris* bat in her care. The virus that was isolated was compatible with this bat species (46,47). The second case occurred in a 37-year-old female who developed rabies in 1998, approximately 27 months after presumable exposure from a bite by an unspecified flying fox. This isolate belonged to the pteropid ABLV variant (48,49).

Filoviruses in bats

Filoviruses, such as Lake Victoria Marburg virus (MARV) and Ebola virus (EBOV), cause severe hemorrhagic fever with a high fatality case rate in humans (80–90%). Furthermore, they are easily transmitted between humans, and several significant outbreaks were reported from sub-Saharan Africa (50–52). The index cases of MARV infection occurred during 1967 among laboratory workers in Germany and the former Yugoslavia, who handled tissues and blood of African non-human primates (53). However, the natural reservoirs of filoviruses have been unknown for many years, in spite of significant international efforts to determine their natural relationships. Until recently, these viruses were identified only in moribund humans and apes. The situation changed between 2001 and 2005, when antibodies to EBOV were detected in four species of tree-roosting fruit bats from Gabon: 4 of 17 *Hypsignathus monstrosus*, 8 of 117 *Epomops franqueti*, and 4 of 58 *Myoncteris torquata*. Viral RNA was detected in the liver and spleen of other bats from the same populations: 4 of 21, 5 of 117, and 4 of 141, respectively (50). However, no direct link between human disease and bat exposure could be established. More recently, an epidemiologic investigation putatively linked the index case of EBOV outbreak in the Democratic Republic of the Congo (DRC) in 2007 to a contact with freshly killed fruit bats, which were migrating in close proximity to the outbreak villages and represented an important food source for local people (54).

Furthermore, retrospective analysis demonstrated that the majority of human cases of MARV infection could be linked to visitation of caves and mines. Recently, it was reiterated by fatal cases of MARV infection in tourists who

visited caves in Uganda where multiple bats were present (55,56). Surveillance of a variety of animals, collected in the Durba mine (DRC) during the MARV outbreak, demonstrated the presence of MARV RNA in insectivorous bats from the *Rhinolophus* and *Miniopterus* genera and in Egyptian fruit bats (*Rousettus aegyptiacus*), but not in animals from many other taxa including vertebrates and invertebrates (51). Similarly, MARV RNA was detected in *R. aegyptiacus* from Gabon, Uganda, and Kenya, whereas in other bat species it was detected only occasionally. Moreover, in Uganda, infectious virus was isolated from *R. aegyptiacus* with a high RNA load detected by the polymerase chain reaction (PCR). Gene sequences of MARV strains identified in bats were identical to those in humans (52,57,58).

However, the detailed ecology of filoviruses is still unknown. Reports on seroprevalence in bats are somewhat controversial. Colonies of *R. aegyptiacus* in caves often consist of tens of thousands of bats (Fig. 2). The opportunity for conspecific exposure rates in such colonies appears quite high and, therefore, bat populations should have a significant seroprevalence rate to these viruses. For example, seroprevalence to lyssaviruses in some colonial bat species was reported as high as 60–70% (35). In contrast, the seroprevalence of MARV neutralizing antibodies in colonies of *R. aegyptiacus* where PCR-positive bats were collected was only approximately 12% or as low as 2.4% (52,57). It is still unclear whether bats are the principal reservoir hosts of filoviruses, or if they represent a spillover infection from some other source. In fact, the identity of gene sequences from bat and human isolates does not necessarily mean that humans were infected from bats. Potentially, bats and humans could be independently and simultaneously infected from some other source in mines and caves.



Fig. 2. A dense colony of the Egyptian fruit bats (*Rousettus aegyptiacus*) in cave (Photo by Ivan V. Kuzmin).

Presently, it appears that the likelihood of filovirus spillover into humans is limited. Nevertheless, as transmission mechanisms and the sources of such spillover infections are poorly understood, public awareness must be increased, and health authorities informed about the documented and suspected presence of filoviruses in bats. Enhanced ecological and epidemiological study of wildlife, such as bats and their associated pathogens, will assist in the eventual prevention and control of these highly pathogenic EIDs.

Henipaviruses and other paramyxoviruses: a recent emergence with severe consequences

In 1994, at the Brisbane suburb of Hendra, Australia, infection with a previously undescribed member of the *Paramyxoviridae* family caused the deaths of 13 horses and one human from an acute respiratory disease (59,60). The virus, known initially as equine morbillivirus, was later renamed Hendra virus (HeV). Thereafter, in 1995, a farmer from Mackay, in Queensland, developed fatal HeV encephalitis, attributed to exposure to two HeV-infected horses that had died more than a year ago (61,62). The HeV outbreak stimulated enhanced surveillance to find the natural reservoir of the virus. Fruit bats (*Pteropus* spp.) were found to have a high seroprevalence to HeV, indicating that they may be a wildlife reservoir. Serological evidence of HeV infection has not been found in any animal species, other than bats in the *Pteropus* (so-called flying foxes) genus (63,64). As was demonstrated experimentally, *Pteropus* bats develop subclinical infection after inoculation with HeV with transient viremia (65,66).

Another related paramyxovirus, Nipah virus (NiV), was first recognized in a large human outbreak that affected 283 persons and caused 109 deaths in Malaysia during 1999. The outbreak was preceded by a large NiV outbreak among pigs, which resulted in a culling of over a million swine (67,68). Genetic similarity between NiV and HeV suggested creation of the *Henipavirus* genus within the viral family *Paramyxoviridae* (69) and a search of NiV reservoir among fruit bats. Antibodies against NiV virus were identified in two native *Pteropus* species in Malaysia (70). The virus was subsequently isolated from urine samples from a *P. hypomelanus* colony on Tioman Island (71). The initial porcine outbreak was thought to be caused by transmission of NiV from fruit bats to pigs. One of the scenarios suggested that an infected fruit bat might drop a piece of contaminated fruit within a pig sty or, alternatively, an infected sick or dead bat might be eaten by pigs.

Further antibodies to NiV were detected in *Pteropus* bats from Cambodia, Thailand, China, and Bangladesh (72–75). In Bangladesh, several severe outbreaks of NiV encephalitis in humans were documented starting from the early 2000s, with case fatality rates about 70–90%. In

a few initial outbreaks, contacts with sick livestock were suggested as a source of the infection, whereas for other outbreaks direct transmission of NiV from *Pteropus giganteus* bats to index cases was suggested via consumption of contaminated fruits or drinking of contaminated date palm sap with further human-to-human transmission (74,76,77).

In 2001, an outbreak of febrile illness in humans, associated with an altered sensorium, was observed in Siliguri, India. Laboratory investigations at the time of the outbreak did not identify an infectious agent. Because Siliguri is in close proximity to Bangladesh, where outbreaks of NiV infection were recently described, clinical material obtained during the Siliguri outbreak was retrospectively analyzed for evidence of viral infection. The presence of NiV antibodies and RNA were detected in ~50% of the patients. As in Bangladesh, direct human-to-human transmission was observed between family members of the patients and hospital staff (78).

The distribution of *Pteropus* bats is limited to islands of the Pacific and Indian Oceans and continental areas from Pakistan east across Southeast Asia to Australasia. By inference, this area might be considered enzootic for henipavirus distribution. However, recent discoveries changed this interpretation. Antibodies to NiV were detected in several fruit bat species in Madagascar including *Pteropus rufus*, *Eidolon dupreanum*, and *Rousettus madagascariensis*. The two latter species are not members of *Pteropus* genus and their exposure to NiV might occur via contact with *P. rufus* (79). However, later seroprevalence to henipaviruses was detected in 22–39% of *Eidolon helvum* fruit bats from Ghana, out of the *Pteropus* genus range (80). Moreover, divergent henipavirus RNA was detected in fecal samples of these bats. One of the obtained gene sequences was most related to NiV and another two represented novel genetic lineages within the *Henipavirus* genus (81). This is remarkable because *E. helvum* is highly abundant in sub-Saharan Africa and form large colonies, which conduct annual transcontinental migration following the rainfall gradient to suitable feeding grounds (82). These animals frequently roost in urban settings and, in several African countries, are routinely hunted and consumed by humans as a supplementary source of protein.

During the search for NiV on the Tioman Island, two other bat viruses were isolated in addition to the NiV, which was the main target. These were Tioman virus and Pulau virus (83,84). Tioman virus was a novel paramyxovirus in the genus *Rubulavirus*, whereas Pulau virus was a novel reovirus in the genus *Orthoreovirus*. At the time of discovery, both viruses were orphans in terms of their significance for veterinary and public health.

In 1997, during the investigation of a swine disease outbreak a new paramyxovirus, named Menangle virus,

was isolated from stillborn piglets with deformities at a large commercial piggery in New South Wales, Australia (85). Serological investigation of persons in contact with pigs revealed that two humans, who were in close contact with infected pigs and suffered an influenza-like illness, had high levels of neutralizing antibodies to Menangle virus (86). Antibodies to Menangle virus were detected in all four species of flying foxes in Australia (87).

Molecular and antigenic studies indicated that Tioman virus is very closely related to Menangle virus, which indirectly confirmed the bat origin of Menangle virus (83,88). The potential of Tioman virus to infect and cause disease in human or other animals is unknown. However, recent studies have demonstrated that pigs are susceptible for infection by Tioman virus (89) and that there is serological evidence for infection of humans by this virus on Tioman Island (90).

SARS-like and other coronaviruses in bats

Severe acute respiratory syndrome (SARS) emerged during November 2002 in southern China, and a SARS coronavirus (SARS-CoV) was identified as the etiologic agent (91). This epidemic, and the identification of SARS-CoV in animals, associated with the wildlife trade in southern China particularly in civets and raccoon dogs (92) stimulated increased CoV surveillance. As demonstrated from the outbreak, none of the suspect animals were a direct source of SARS-CoV. Furthermore, surveillance led to identification of SARS-like CoVs in horseshoe bats (*Rhinolophus* spp) in China. These CoVs shared similar genomic organization and identity with SARS-CoV, except for the spike protein gene S, which is responsible for binding to the receptor on susceptible cell surface (93,94). The level of nucleic acid sequence difference (~8%) from SARS CoV in multiple genes was too great for SARS-like CoV in *Rhinolophus* bats to be the parent to the outbreak virus. The presence of multiple SARS CoV-like viruses, the inability to detect SARS CoV-like viruses in other species of wild animals, and the detection of a wide range of other coronaviruses in bats suggests that bats are a rich source of CoVs, however, the evolutionary pathway of SARS-CoV remains to be fully identified.

Further surveillance and characterization of bat CoVs identified close members of many known mammalian CoV species as well as several species exclusively present in the bat. These studies revealed high genetic diversity bat CoVs across a large geographic distribution. Moreover, the same species of bat from different geographic locations can also contain the same type of CoV (95). In China, high CoV prevalence was detected in the *Vespertilionidae* and *Rhinolopidae* families of bats. The overall prevalence was about 6%, but in certain bat colonies it was as high as 35–55%. Such diversity was significant and not only SARS-like CoVs (from *Betacoronavirus*, former

group 2) but also additional putative novel subgroups from *Alphacoronavirus* (former group 1) were identified in bats (96). Similar results were reported from Hong Kong (97). Further studies demonstrated that CoV-positive bats appeared healthy, with only a limited reduction of body weight, with viral clearance occurring between 2 weeks and 4 months (98). In addition, the authors reported that co-infection of the same bat species by two different coronaviruses, a SARSr-Rh-BatCoV Rp3 from Guangxi, China, and a Rf1 from Hubei, China, may have allowed the opportunities for recombination via a breakpoint at the nsp16/spike region and possibly generated a recombinant virus—the Civet SARSr-CoV.

After the discovery of SARS-like CoVs in bats in Asia, a number of bat CoVs were identified in Europe, North America, South America, Australia, and Africa with an overall prevalence of 9 to 20%. In Europe, the alphacoronaviruses and betacoronaviruses, identified in *Vespertilionidae* bats, were genetically similar to the CoVs identified in bats from China (99). In the United States, 17% of *Eptesicus fuscus* and 50% of *Myotis occultus* were positive for CoVs. Phylogenetically these viruses belonged to the same alphacoronavirus group but formed distinct clusters from Asian CoVs (100). In Canada, an alphacoronavirus identified in *Myotis lucifugus* bat is probably a variant of alphacoronaviruses identified in *Myotis occultus* in the United States. In South America, the Trinidadian CoVs identified in *Phyllostomidae* bats were clustered with alphacoronavirus from North America. In Africa, enhanced surveillance demonstrated significant divergence of CoVs in bats from Kenya (101). In that study, SARS-like CoV was identified in a *Chaerephon* sp. bat (*Molossidae*). Furthermore, in contrast to China and Hong Kong, various CoVs were detected in bats from the families *Hipposideridae* and *Pteropidae*. Overall CoV prevalence in Kenya bats was approximately 19%, and CoV diversity was greater compared to that documented in Asia, Europe, North and South Americas, and Australia.

In general, the diversity of CoVs in bats appears greater than in other animals tested to date. This observation suggests that bats are likely the primary hosts of this viral family. Because attempts to isolate CoVs from bats by multiple international groups have failed and only viral RNA was detected (predominantly in fecal swabs), this limitation significantly reduces the possibility to investigate CoV pathobiology, evolution, and adaptive mechanisms *in vitro* and *in vivo*.

Bats: are they special?

Why are bats the reservoirs of so many EIDs? Bats have several unique features that may account for their importance in EID transmission and maintenance. Bats are the second largest order of mammals. Currently, there are ~1,200 recognized bat species worldwide, accounting

for approximately 25% of all mammalian species (102). The diversity of bat species alone, along with their worldwide distribution, contributes to the biodiversity of their pathogens.

Bats are unique in their mobility as they are the only mammals capable of flight, allowing them to transmit EIDs during their foraging flights and during seasonal migrations. This extensive mobility, coupled with roosting plasticity and broad food range, means that bats could transport viral material to many different animal species in various locations per unit time (103).

The ability to fly also has immunological implications. Flight requires a low body mass and bats have evolved to have hollow bones to decrease their body mass. The hollow bones allow them to fly, but as a result they do not have bone marrow as similar to non-volant mammals and must produce B-cells in different locations (104). Whereas basic immunological commonalities are shared among all mammals, certain unique anatomical and physiological parameters peculiar to bats may also help to explain the plethora of agents associated with this mammalian order.

Besides their ecological vagility, bats are considered one of the most social groups of mammals (Fig. 2). Many bat species roost together in very large and dense colonies. This dense clustering of individuals provides ample opportunities for viral exchange within bat populations (103). Bats with high levels of interspecies contact, such as *Myotis*, have been found to harbor a diverse range of RABV, suggesting that increased contact between species increases viral transmission (105). Several infectious agents, including NiV, have been isolated from the urine of fruit bats and during mutual grooming fur contaminated by urine may allow for viral transmission between individuals (68,106).

Regarding ecological flexibility, bats inhabit a wide variety of ecological niches. Some species are flexible in roost preferences, including caves, trees, and many man-made structures, other are more restricted to specific roosting. The ability of bats to occupy man-made structures is of particular importance, because it increases the opportunities for interactions between bats, domestic animals, and humans. For example, the big brown bat (*Eptesicus fuscus*) and the serotine bat (*Eptesicus serotinus*), both of which are known to harbor lyssaviruses, commonly roost in man-made structures. Bats often inhabit and feed in agricultural areas, which brings them into closer contact with humans and domesticated animals. In the tropics, frugivorous bats can be found roosting urbanistically and feeding on fruit trees in plantations (107).

Not only are bats able to inhabit a variety of diverse locations, but they also have a number of trophic specializations. The majority of bat species are frugivorous or insectivorous. In addition, three bat species, all found in Central and South America, are hematophagous

(vampire bats). These dietary habits affect rabies transmission risks as described above. Depletion of environmental resources and urban expansion into bat habitats can deplete natural food sources. When their natural food sources are scarce, vampire bats will switch preferences and feed on humans and domestic animals (14). Frugivorous bats often leave behind half-eaten fruits that may be contaminated with viral particles from their saliva; if the viral levels are high enough, an animal may develop infection following consumption of these fruits. It is hypothesized that the consumption of half-eaten fruits may have caused the transmission of NiV from fruit bats to pigs and humans, as well as sharing of the raw date palm sap from the tree collectors (67,68,76,77). Similarly, insectivorous bats will discard contaminated insect parts, which can then be consumed by foraging animals (107), although mechanisms for such route of pathogen transmission from insectivorous bats has not been corroborated to date. Omnivorous bats, such as *Phyllostomidae*, will consume nectar, plants, arthropods, and small vertebrates as food sources as necessary. This ability to utilize a wide variety of food sources may lead to increased biodiversity in a small area, enhancing the opportunities for multiple species to interact and share infectious pathogens. Environmental factors can shape pathogen transmission and spillover into a new species as well; periods of resource limitation may bring together diverse species. During the dry season, primates and bats may come into closer contact as they search for limited food supplies, enhancing opportunities for cross-species transmission of filoviruses (107).

Although their mobility, sociality, and ability to inhabit a variety of niches likely influence the importance of bats as sources of EIDs, there are some additional characteristics of bats that may contribute into this phenomenon. For example, Microchiroptera possess the ability to echolocate, to produce laryngeal vocalizations for navigational purposes. Echolocation may cause aerosolization of viral particles in the nasal mucosa and saliva, enhancing transmission to other individuals (4). However, this mode of transmission has not been experimentally verified to date. Additionally, when adjusted for body mass, Chiroptera are the longest-living mammalian order (108). Although long-term viral persistence in bats remains to be determined, a long-lived carrier would have even more opportunities to transmit the infection within bats populations and to other species.

The long evolutionary history of bats may also play a role in their association with EIDs, because of long co-evolution between bats and the viruses. Pathogens could have evolved to utilize cellular receptors that are conserved across a wide range of animal species, providing a mechanism for interspecific infections (4,109). For example, henipaviruses are capable of infecting species in

six mammalian orders and SARS-CoV uses an enzyme receptor that is conserved among animals (109).

The specific immunological parameters that are involved in agent evolution leading to persistence or perpetuation of EIDs in bat populations are not fully understood. Recent studies have examined innate, antiviral, and interferon genes from several species of bat, and suggest that certain alleles may be associated with increased parasite burden (110). Cells expressing surface immunoglobulin were identified in *Pteropus* indicating that lymphoid development in bats, as well as immune system components, like IgG, IgM, IgA, macrophages, B- and T-lymphocyte-like cells, are similar to other mammals (111,112). In studies examining leukocyte response to the phytohemagglutinin (PHA) skin test, a technique used to measure delayed-type cellular immune response in many vertebrates, diverse leukocyte traffic was observed in the 6–24 hours following PHA injection (113). Bat interferon alpha and beta are homologous to other mammalian interferons, but there is low homology of these interferons specifically between bats and humans, which could indicate different antiviral activity between the two and contribute to the high pathogenicity of bat agents in humans (114).

In addition, recent sequencing of genome fragments to infer genes within the interferon alpha family in both *Pteropus* and *Myotis* bats has revealed that both have up to 24 IFNW genes, while humans, mice, and pigs have only one (115). The enormous size of this gene family within bats compared to other mammals suggests that it may still be involved in host immune defense, even though its function may have been lost in other vertebrates. He et al. (116) suggested that the bat interferon alpha gene family is under positive selection, which most likely reflects an evolutionary arms race, between pathogens evolving to block immune recognition and host immune systems responding to maintain effective response to these pathogens. However, based on latitude, some bats undergo hibernation during winter, which has been shown to decrease levels of neutrophils, monophils, and lymphocytes, leading to immunosuppression in other small mammals (117). If so, how do related infectious agents overwinter in bats? These and many other questions about basic bat immunology and pathobiology of bat-adapted pathogens still remain unanswered. Serological assays have shown though that some virus specific adaptive T- and B-cell responses do occur, despite the suggestion of persistent infection with viruses including HeV, SARSs-CoV, and EBOV (reviewed in Calisher et al. (4)). In addition, bats are capable of harboring large numbers of genetically diverse viruses within a geographic location and within a taxonomic group (118). Several viruses for which bats act as a reservoir, including the paramyxo-, filo-, and rhabdoviruses, appear phylogenetically related and grouped in the order Mononegavirales,

possibly indicating a more fundamental connection between bats and these specific RNA agents (119).

Persistence or perpetuation of bat-associated EIDs

The essential pathobiology of bat agents contributes inherently to their persistence or perpetuation in reservoir individuals, colonies, and populations. Based on current research, there is very little evidence to suggest that any of the major bat-associated EIDs persist within the host, and it is therefore most likely that these viruses are maintained in nature by perpetuation within and between bat colonies and through multiple spillover events into other hosts due to the extreme mobility and highly social nature of the bat hosts. Among these various agents, lyssaviruses have been most thoroughly characterized. For example, RABV, the representative species of this genus, perpetuates through bite transmission between infected animals. In essence, RABV is characterized by a rather low basic reproductive rate and a short infectious period. Bats mount both an innate and adaptive immune response to peripheral RABV infection. Helper and cytotoxic T-cells activate upon infection, to recognize and clear the virus both outside and inside of infected cells. However, once the virus reaches the CNS, the host adaptive immune response is less able to clear infection.

Pathogenic RABV may limit its replication rate and produce fewer infectious particles to completely evade, or only minimally activate, the peripheral host response. Single exposures do not always confer protection against successive infections, leading to perpetuation in bat populations, but repeated exposure has been shown to provide long-term immunity (up to a year) and reduced susceptibility (120). These findings have been corroborated by other studies that show that colony-wide mortality does not increase significantly after episodes of infection with EBLV-1 (121).

In affected bat colonies, a relatively low point prevalence of rabies infection has been usually observed, varying from <1 to 4%. In contrast, prevalence levels of RABV-neutralizing antibodies have been documented between 65 and 70% (reviewed in Kuzmin and Rupprecht (7)). In bats, cave colonies show strong seasonal fluctuations with increased seroprevalence in adult females and juveniles directly following parturition (122). These seasonal shifts may be due to the birth pulse, adding large numbers of susceptible juveniles into the population and increased contact rates between adult females and pups while nursing. Recently, employing a model that integrated immunological parameters, epizootiology, and disease demography, Dimitrov et al. (123) showed that total colony immunity is actually strengthened by perpetuating RABV infection. This model predicted that low removal rates of infected individuals (due to death) led to a colony with a stronger total immune profile while

high removal rates, like that seen in other carnivores, led to the epizootics normally associated with RABV.

Little is known about how NiV and HeV are maintained in bat populations. These viruses encode V proteins that bind to signal transducer and activators of transcription 1 (STAT1) and STAT2 proteins of host cells to block alpha, beta, and gamma interferon responses (124–126). Such V proteins may facilitate evasion of the host immune system, although it is not well known how viral proteins will affect potential interferon responses to virus infections in bats. The NiV V protein can prevent IFN signaling in cells from multiple species and other proteins may also have specific activities (126). The presence of multiple anti-IFN mechanisms may relate to the zoonotic nature of henipaviruses but this remains to be explored in Pteropodid bats, which are seemingly natural reservoir of these viruses have likely passed a long-term co-evolution.

Ecological studies suggest that NiV spillover events may fluctuate seasonally. All outbreaks, with the exception of the initial spillover event in Malaysia, occurred during the first 5 months of the year (74–78). Wacharapluesadee et al. (127) found that this time period coincided with the time in which the greatest amount of viral RNA could be recovered from wild populations of *Pteropus lylei*. Horizontal transmission via urine, feces, and saliva is thought to be the primary route of intra-specific and spillover infection for HeV (128,129). Spillover events of HeV into horses are associated with the flying fox birthing season, when pregnant and lactating females are at a higher risk for HeV infection (reviewed in Halpin et al. (130)). These events are hypothesized to occur through contact with either infected birthing material or exposure to an increased number of infected individuals. Models of HeV infection dynamics suggest that the pathogen is not endemic in local populations, but persists broadly due to meta-population dynamics. Further, it has also been hypothesized that immunity in *Pteropus scapulatus*, the principal reservoir of HeV, wanes over short time scales and this could enhance the persistence of infection in *P. scapulatus* populations. Nutritional stress in response to decreases in fruit and nectar availability has also been associated with increasing risk of transmission (128,129).

In fact, bats were not the direct origin of the human SARS epidemic but the diversity of bat coronaviruses is fascinating. Modes of perpetuation of CoVs have not been established, but an increase in prevalence within lactating adult female bats has been demonstrated for several vespertilionid species (99). As has been recently shown, bats experimentally infected with CoV did not develop clinical signs of disease, although viral RNA was detected in their intestines and feces. In addition, reduced susceptibility of bats to a CoV isolated from another bat species has been demonstrated, suggesting that certain

CoV variants are well adapted to certain host species (131).

Although both EBOV and MARV are hypothesized to have a bat reservoir, no conclusive evidence has been obtained to date. Though it is not known if or how EBOV persists in bat populations, trends in great ape mortality suggest the seasonal component. Death rates of great apes have been observed to increase at the end of the rainy season, which may lead to increased contact rates between apes and other animals, including bats, competing for food (132–134). However, contacts between bats and apes have also been observed during the dry season when fruit is abundant and many animals share the same food source locations (50,135).

Making ourselves sick: drivers of bat-associated EIDs

As with other zoonotic EIDs, emergence of diseases from bat reservoirs is primarily associated with ecological changes that influence the host or parasite. More specifically, changes that increase the duration or frequency of host-pathogen interaction give rise to greater opportunities for transmission (119). The underlying causes of bat EIDs can be organized in a hierarchical fashion (Fig. 3) as macro-scale societal changes lead to increased animal/human interactions, which in turn lead to increased disease emergence. Bat-associated EIDs appear as a ‘tip of the iceberg’ regarding a much more dynamic complex of interacting variables.

The pathways of disease transmission between bats, peridomestic/domestic animals, and humans are summarized in Fig. 4. Although we are predominantly concerned with human pathogens, it should be noted that infectious diseases emergence also occurs in non-human hosts, including bats themselves, as a result of ecological changes brought by human activity. For example, the recent epizootic of White Nose Syndrome (WNS) among several bat species in the Northeastern United States may be due to the translocation of a fungus from Europe to North America by humans (136). Furthermore, it is highly probable that the emergence of pathogens in bats also occurs via contact with domestic/peridomestic animals. However, evidence in support of this pathway is limited due to lack of research in this area.

The primary drivers of bat-associated EIDs include overpopulation, environmental degradation, and socio-economical forces. The emergence of new pathogens is associated with growth and increased density of humans and other mammals. In recent history, the human population has exploded, with an increase from 1 billion to 6.8 billion in the past 110 years. As populations grow, humans begin to inhabit previously untouched, often biodiverse areas. Research suggests that diseases are more likely to emerge in such regions (2). Coupled with this is

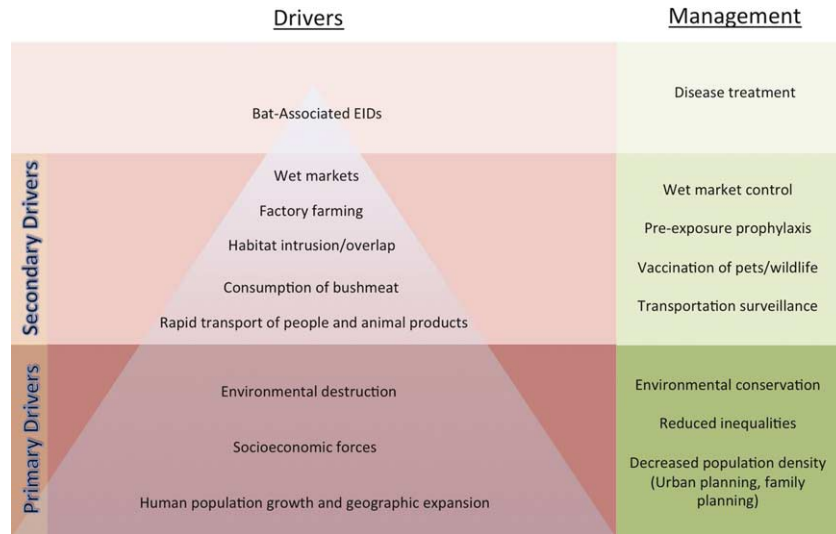


Fig. 3. Diagram of primary and secondary drivers and management of bat-associated EIDs.

the increased utilization of natural resources to meet the human demand for food and support consumption of goods.

Environmental degradation causes habitat disturbance and reduction, resulting in changes in species range and density. For example, land use changes such as mining and deforestation for farming and the construction of human habitats in the Amazon Basin have likely contributed to the re-emergence of vampire bat-derived rabies in humans. In 2004, at least 46 deaths were caused by vampire bat rabies (predominantly in Brazil and

Colombia), whereas only 20 cases were transmitted by dogs in all of Latin America (137,138).

Economic forces unquestionably fuel environmental destruction. Much of the deforestation and habitat intrusion in the Amazon, for example, is a result of the increasing demand for oil and minerals. Moreover, economic forces contribute to secondary drivers such as increased transportation, agricultural practices, food availability, and choice regarding food consumption. Socioeconomic inequalities, meanwhile, perpetuate disease transmission through disparities in health care

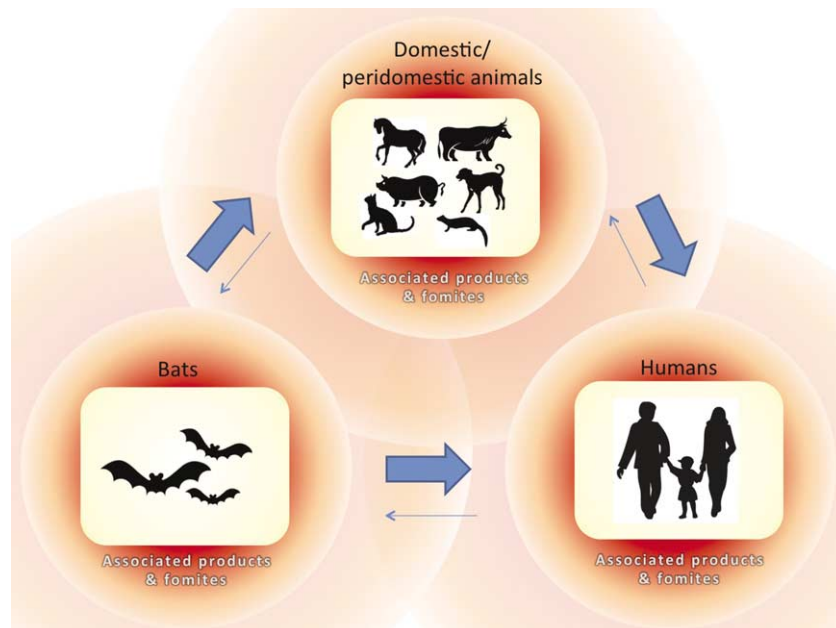


Fig. 4. Possible routes of disease transmission between bats, peridomestic/domestic animals, and humans. Thick arrows represent the most significant pathways for bat-associated EIDs. Thin arrows represent pathways about which less known or that are less common (as in the case of transmission of pathogens directly from bats to humans).

access, education, food security, and access to clean water. In addition, the increase in human population density and mobility, together with environmental destruction and economic forces, are also contributing to pathogen emergence. These primary drivers not only contribute to risk by increasing the abundance of human hosts, but also fuel more immediate causes of disease emergence such as those discussed below.

Economic prosperity has led to advances in technology, which has fostered the development of an expansive global trade network. Increased mobility of people, animals, and goods allows for the rapid spread of novel diseases and outbreaks of existing diseases. The cross-continental spread of infectious disease is most likely to occur through air travel (139), while local transportation networks may be important for sustaining epidemics within continents (140). For example, the SARS outbreak was first reported in Guangdong, China in November of 2002 and within months a cluster of cases appeared in Hong Kong (141). Due to air transit, SARS cases were reported as far away as Canada (in addition to several Southeast Asian countries) by the end of March of 2003 (142). As previously mentioned, the spread of WNS throughout bat populations may serve as an example of how human movement also influences the emergence of EIDs in wildlife (136).

Large societal changes have led to smaller, more regional phenomena that increase the emergence of infectious diseases. For example, ecotourism likely increases the rate of disease exposure through the direct intrusion of humans into wildlife habitats (such as recent cases of MARV infection in tourists after visitation of caves in Africa (55,56), or DUVV infection of a tourist bitten by a bat during a safari trip (44)).

Human practices surrounding the production and consumption of food can contribute significantly to the risk of new pathogen emergence. For example, wet markets (in which live animals are sold and butchered on the spot) are an ideal environment for microbial exchange due to the high density of people, and the diversity of wild and farmed animals sold at these sites. Live animal markets appear to have contributed to the emergence of SARS in China in 2002. With primary bat origin, several intermediate hosts have been suggested (such as Chinese ferret-badgers, *Melogale moschata*, and raccoon-dogs, *Nyctereutes procyonoides*), although palm civets (*Paguma larvata*) are suspected to be the most important for the transmission of the virus to humans (92). In Southern China, civets are both hunted and farmed for eating. In fact, civets tested in wet markets have a higher rate of seropositivity for SARS than those tested on farms, suggesting that the markets may serve as centers for viral transmission (143). In addition, food handlers and persons employed at wet markets are more

likely to be seropositive than those with other occupations (144).

Consumption of bush meat is known to amplify the risk of pathogen emergence and this is also true for the transmission of bat-associated EIDs. Epidemiological evidence suggests the direct transmission of EBOV from bats to humans in the Democratic Republic of Congo, where the migratory fruit bats, *Hypsignathus monstrosus* and *Epomops franqueti*, are hunted and sold in markets for consumption (54). Additionally, *Eidolon helvum* fruit bats, a natural reservoir for LBV and henipaviruses, are consumed in several regions of West Africa (80).

Furthermore, agribusiness has overshadowed small-scale farming across the globe, particularly in Southeast Asia. Industrialized agriculture involves the mass-production of a single species of animal or plant. Monoculture increases susceptibility to pathogens due to the widespread availability of hosts of the same species. This is exemplified by the NiV outbreaks in Malaysia during 1998–1999. Deforestation and the increased farming of pigs and fruit-producing trees are suspected to have contributed to the swine infection with NiV. Of course, the intensification and expansion of agriculture is a serious concern throughout the world, as it is a driver of many other EIDs (not associated with bats), the most notorious of which are the avian influenza viruses.

Ironically, the achievements of human civilizations over the past century have been the indirect drivers of new classes of zoonotic diseases. These issues are not only difficult to solve, but they are also expensive and politically unpopular to address, as human economic progress is often in inherent conflict with environmental conservation.

Pathogen emergence occurs as a result of complex interactions of many factors, requiring a multidisciplinary approach to research and prevention. The drivers of disease emergence are studied by professionals trained in fields as diverse as disease ecology, anthropology, geography, economics, wildlife population biology, and wildlife veterinary medicine (1–3). A better understanding of drivers of EID emergence is essential to inform effective policies that address both the immediate and underlying causes of disease emergence.

Control and prevention of bat-associated EIDs

The previous section focused on the mechanisms that drive disease emergence from bats, progressing from primary to more proximate factors. This section will examine control in the opposite direction, progressing from the individual level, proceeding through population-wide approaches, and ending with society-wide suggestions for primary prevention of bat-associated EIDs.

At the individual level

No specific medical therapy has proven beneficial once people become ill from bat EIDs (at least of viral origin). For example, although rabies is an ancient disease, effective therapeutic treatment of rabies in humans continues to be very challenging. Rapid early diagnosis in the biting animal is critical, since identification of rabies before its fulminant stage allows for effective prophylaxis. Fulminant rabies continues to carry a very poor prognosis. The first case of the successful experimental treatment of rabies in a naïve patient was a 15-year-old girl bitten by a bat in 2004 (145). However, extension of the ‘Milwaukee Protocol’ (i.e., therapeutic coma, antiviral drugs, intensive medical care) in other patients has been much less successful (see for example Rupprecht (146) and Rubin et al. (147)).

Prophylaxis, after exposure but well in advance of illness, has a much higher success rate. Appropriate post-exposure wound cleansing has been shown to reduce significantly the likelihood of RABV transmission (148). Besides washing the wound with soap and water, unvaccinated persons should receive both rabies immune globulin and four doses of cell-culture vaccine. Globally, more than 12 million persons receive post-exposure prophylaxis each year (149).

Besides rabies, novel treatment strategies are being developed for other bat EIDs. The use of RNA interference has been suggested for the treatment of henipaviruses (150). These currently untreatable infections may be ameliorated by the introduction of small interfering RNA molecules homologous to the RNA in these pathogens. While promising in theory for many agents, this line of treatment is still in its preliminary stages, and issues such as efficacy in humans, delivery, and cost have yet to be addressed.

The potential for filoviruses to be used as bioweapons has spurred research efforts for an effective vaccine that could be used in an outbreak. For example, in a mouse model of hemorrhagic EBOV infection, a vesicular stomatitis virus-based vaccine has been shown to be safe and effective in preventing clinical presentation of disease (151). Furthermore, the possibility that this vaccine may be deliverable through mucosal surfaces offers potential as a rapid vaccination agent during an outbreak.

At the population level

At the population level, rabies is the quintessential bat EID that has been studied most intensively. Public health guidelines recommend rabies vaccination for humans in high-risk groups, vaccination of pets as well as animals on public display, isolation of domestic animals from the wildlife reservoirs of rabies, and public health education on appropriate precautions. Current guidelines recommend that pre-exposure prophylaxis be offered to those in

high-risk groups including veterinarians, animal handlers, rabies researchers, and some laboratory workers. In addition, the vaccine can be offered to long-term travelers to endemic areas, especially if immediate medical attention will be unavailable (148,152). Routine vaccination of the general population is currently not recommended, mostly due to cost.

Despite advances in determining best practices for animal vaccination, control of rabies in domestic and wild reservoirs remains challenging in resource-limited settings. Control of rabies in bats has proven challenging. Bat rabies has been reported in every state except Hawaii and 1,806 rabid bats were documented in the United States during 2009 (19). Of all animals, bats in particular pose a serious risk for rabies and should be excluded from structures to prevent contact with humans (148,152). However, widespread reductions in bat populations to control rabies is neither feasible nor desirable. Instead, some novel methods have been explored to control infection in bat populations. Vampire bats can efficiently digest only coagulated blood and they die if the consumed blood is not coagulated. Application of anticoagulant-containing ointment on the fur of captured vampire bats (with their subsequent release) leads to consumption of the coagulant by several roost mates via mutual grooming. Similarly, anticoagulation of livestock is another useful approach to control vampire bat populations where rabies is a threat (reviewed in Kuzmin and Rupprecht (7)). As another approach, it has been suggested that oral vaccination of wildlife may limit the spread of rabies by bats (153). Finally, we know that some species of moths are able to disrupt bat echolocation using ultrasonic clicks of their own (154,155). The use of similar, artificially produced, sounds to ward off bats from human and livestock habitats should be explored.

At the societal level

The recent emergence of SARS coronavirus and Henipavirus from bat reservoirs has spurred thinking on how to control future disease emergence. As we noted in the previous section, the primary drivers of emergence are growing global mobility, environmental degradation, and overpopulation.

We may be able to confront the threat presented by increased global mobility with practical measures such as transportation surveillance. Monitoring ports and borders for ill passengers and animals and providing care to them would not only benefit the ill, but also the populations they are moving into. Likewise, pre-trip vaccinations and post-trip health monitoring not only benefit the international travelers but also the population to which they return.

Environmental conservation has long been the domain of those hoping to preserve biodiversity and the magnifi-

cence the natural world. Given the emerging evidence that environmental degradation leads to increased rates of disease emergence, it may be time for those in the public health field to also advocate environmental conservation. Since the effects of environmental degradation on disease emergence are still not fully understood, increased funding of research in this field is also sorely needed.

Conclusions

The international attention to newly emerged or discovered bat-associated EIDs has increased dramatically during recent decades. The above brief review of recent history highlights that pathogen discovery has been accomplished in very different scenarios, from accidental detection of 'orphan' viruses to the confirmation of bat origin of known diseases using targeted surveillance. Moreover, although this brief review has focused upon the relationship of bats and emerging viruses, a number of other diverse agents are also associated with bats including bacteria such as *Bartonella* (156), and long-standing relationships with certain fungal diseases such as histoplasmosis (157). It is anticipated that, with the advance of modern molecular tools and increased scientific activities in this field, additional bat EIDs with public health, veterinary, and conservation implications will be uncovered and better understood with practical effective prevention and control modalities necessary for application in the near future.

Disclaimer

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