

Emerging infectious diseases associated with bat viruses

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Bats play important roles as pollen disseminators and pest predators. However, recent interest has focused on their role as natural reservoirs of pathogens associated with emerging infectious diseases. Prior to the outbreak of severe acute respiratory syndrome (SARS), about 60 bat virus species had been reported. The number of identified bat viruses has dramatically increased since the initial SARS outbreak, and most are putative novel virus species or genotypes. Serious infectious diseases caused by previously identified bat viruses continue to emerge throughout in Asia, Australia, Africa and America. Intriguingly, bats infected by these different viruses seldom display clinical symptoms of illness. The pathogenesis and potential threat of bat-borne viruses to public health remains largely unknown. This review provides a brief overview of bat viruses associated with emerging human infectious diseases.

emerging infectious disease, bat virus, natural reservoirs

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1 Bat coronaviruses

Members of the family Coronaviridae, within the order Nidovirales, are enveloped, positive-stranded RNA viruses. Several genera have been created for this order of viruses, including *Alphacoronaviruses* and *Betacoronaviruses*, whose members infect mammals; and *Gammacoronaviruses* and *Deltaoronaviruses*, which affect both avian and mammalian species [1,2]. Coronavirus infection usually causes a mild upper respiratory syndrome in humans, however, pathogens that are transmitted zoonotically can be highly pathogenic. This was seen with severe acute respiratory syndrome (SARS) in 2002–2003, which was caused by a novel coronavirus (SARS-CoV) [3,4]. It was demonstrated that SARS-CoV was transmitted to humans from the market civet [5–7]. However, studies of farmed and wild civets did not support the theory that civets were the natural reservoirs

of SARS-CoV [7–9]. In 2005, two independent teams reported the discovery of SARS-like CoVs (SL-CoVs) in bats and suggested that bats are natural reservoirs of SARS-CoV [10,11]. Since then, more genetically diverse SL-CoVs have been found in China, Europe and Africa, suggesting a wide geographical distribution and an ancient origin for these viruses [12–15]. The majority of bat SL-CoVs were found in rhinolopus bats, particularly *Rhinolophus sinicus*, and display 87%–92% nucleic acid identity and 93%–100% amino acid similarity with SARS-CoV [10,11,14–16]. However, those isolates found in Europe and Africa are distantly related to SARS-CoV at a genomic level and possibly represent a new coronavirus species [12,13,16]. Unfortunately none of the above SL-CoVs use the same receptor as SARS-CoV, angiotensin converting enzyme II, to facilitate virus entry into a cell. This suggests that these SL-CoVs are not direct progenitors of SARS-CoV [17]. Phylogenetic analyses support the recombinant origin of a bat SL-CoV coronavirus, and that *R. sinicus* may carry the

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director progenitor of SARS-CoV [18]. Therefore, wide-ranging surveillance of SL-CoVs in bats is needed to determine the origin of these lethal viruses.

In 2012, a disease presenting with acute pneumonia and subsequent renal failure, symptoms similar to those for SARS, emerged in Saudi Arabia. A novel human coronavirus (MERS-CoV, Middle East respiratory syndrome human coronavirus) was suspected to be responsible for this fatal disease. Globally, 64 human cases were confirmed resulting in 38 deaths by June 17, 2013 [19,20]. Phylogenetic analysis showed that MERS-CoV belongs to lineage C of the *Betacoronavirus* genus. It was most similar to the bat coronaviruses HKU4 and HKU5, which infect the lesser bamboo bat (*Tylonycteris pachypus*) and pipistrelle bat (*Pipistrellus pipistrellus*), respectively [21,22]. MERS-CoV exhibits 50% nucleotide identity with the entire genomic sequences of HKU4 and HKU5, and 82% nucleotide identity with the RNA dependent RNA polymerase (RdRp) gene. A recent study confirmed that MERS-CoV uses dipeptidyl peptidase 4 (DPPIV), also known as CD26, as a functional receptor. It has also been shown that this molecule is evolutionarily conserved among mammals, and MERS-CoV can infect a broad range of mammalian cells (humans, pigs, monkeys and bats), suggesting ease of cross-host transmission [23,24]. Whether MERS-CoV was directly transmitted from bats to humans requires further research to confirm.

Human coronavirus 229E (HCoV-229E) and NL63 (HCoV-NL63) belong to the genus *Alphacoronavirus*. These were discovered in 1970 and 2004, respectively, and lead to flu-like symptoms and bronchiolitis [25,26]. In 2009, a bat CoV (Hipposideros/GhanaKwam/19/2008) was discovered in the leaf-nosed bat (*Hipposideros caffer ruber*) in Ghana and was predicted to share a most recent common ancestor (MRCA) from just over 200 hundred years ago with HCoV-229E. A fragment of RdRp in bat CoV Hippo-sideros/GhanaKwam/19/2008 shared 92% nucleic acid identity with HCoV-229E [27]. Most recently, a bat CoV (Bat CoV *Perimyotis subflavus* strain ARCoV.2) was detected in the North American tricolored bat (*Perimyotis subflavus*) and was predicted to share common ancestry with HCoV-NL63; the MRCA between these viruses was predicted to have occurred approximately 563–822 years ago [28]. Phylogenetic analyses of all known CoVs in mammals suggested that bats are ideal hosts for both *Alphacoronaviruses* and *Betacoronaviruses* [1].

2 Bat lyssaviruses

Lyssaviruses are negative-sense RNA, bullet-shaped viruses within the Rhabdoviridae family, of the order Mononegavirales. These viruses cause acute progressive encephalitis (rabies) that is inevitably fatal once clinical signs develop in mammals. There are 12 lyssavirus genotypes: rabies virus (RABV); Aravan virus (ARAV); Australian bat lyssavirus

(ABLV); Duvenhage virus (DUVV); European bat lyssavirus type 1 (EBLV-1); European bat lyssavirus type 2 (EBLV-2); Irkut virus (IRKV); Khujand virus (KHUV); Lagos bat virus (LBV); Mokola virus (MOKV); Shimoni bat virus (SHIBV); and West caucasian bat virus (WCBV) [29]. The link between vampire bat bites and rabies was established at the beginning of the 20th century. Since then, a number of confirmed or suspicious rabies cases have been associated with bats in the USA, Canada, Australia, Latin America, Western Europe and China [29–31]. All lyssaviruses, except Mokola virus, involve bat reservoirs that include fruit bats (*Rousettus aegyptiacus* and *Eidolon helvum*) and microbats (*Miniopterus schreibersii*s, *Tadarida brasiliensis*, *Hipposideros commersoni* and *Myotis* spp.). However, the number of human deaths due to bat rabies remains small compared with those from dog bites in countries with poor sanitary conditions.

3 Bat paramyxoviruses

Over the past decade a number of zoonotic viruses have emerged from flying foxes, and these have been shown to cause serious disease outbreaks in humans and livestock. Hendra virus (HeV) was identified in 1994 as the causative agent of an acute respiratory disease in horses in Brisbane (Australia), and was associated with a single fatality in humans [32]. HeV is naturally hosted by fruit bats (*Pteropus* species), and poses a serious threat to livestock in Australia, with sporadic lethal transmissions to humans almost every year [33]. In 1998 in Malaysia, the closely related Nipah virus (NiV) was found to infect pigs and humans, inducing encephalitis with 40% fatality [34]. Almost every year since, outbreaks of NiV cause severe encephalitis in Bangladesh and India with fatality rate approaching 75% [35]. Multiple rounds of person-to-person NiV transmission have been observed [35,36], increasing the likelihood of NiV infection in humans. In addition to acute infection, these viruses also cause asymptomatic infections that may lead to late-onset or relapsing encephalitis years after the initial infection [37]. Although NiV appears to be most closely related to the morbilliviruses, a few properties of NiV and HeV, including their large genome size, have led to their classification within the *Henipavirus* genus of the *Paramyxoviridae* family [38]. Because of their ability to infect humans, high pathogenicity, wide host range and potent interspecies transmission, HeV and NiV are classified as biosecurity level 4 pathogens.

Apart from viral species that cause fatal diseases in animals and humans in Australia, Malaysia, Bangladesh and India, new distinct viral clades closely related to HeV and NiV have been identified in South Asian and African countries [39–41]. Although many of these pathogens are capable of inducing severe systemic illnesses in diverse terrestrial mammalian hosts, they are comparatively innocuous in

bats [42,43]. Under experimental conditions, it has been shown that the infection of bats with a range of viruses rarely results in disease. Within tissues, low levels of virus are detected, viral shedding is often at the limit of detection, and inconsistent or transient seroconversion is observed [43,44].

4 Bat filoviruses

Filoviruses are associated with acute fatal hemorrhagic diseases of humans and/or nonhuman primates. The Filoviridae family comprises two genera: *Marburgviruses* (MARV) and *Ebolaviruses* (EBOV) [45]. MARV was first identified in 1967 during hemorrhagic epidemics in Germany and the former Yugoslavia following the importation of infected monkeys from Uganda [46]. The five known MARV lineages have been classified as being made up of two viruses, Ravn virus and MARV [47]. EBOV was first identified in the western equatorial province of Sudan in 1976. Five distinct species of EBOV have been identified: *Ivory Coast ebolavirus* (CIEBOV); *Sudan ebolavirus* (SEBOV); *Zaire ebolavirus* (ZEBOV); *Reston ebolavirus* (REBOV); and *Bundibugyo ebolavirus* (proposed) [45]. The Bundibugyo, Sudan and Zaire species have been associated with large outbreaks of Ebola haemorrhagic fever (EHF). These viruses are among the most virulent pathogens known to infect humans. EBOV or MARV outbreaks regularly occur in African countries with a high fatality rate (25%–90%) (<http://www.who.int/csr/disease>).

Bats have been implicated as the reservoirs for MARV and EBOV. Serological and genetic data has shown that these viruses have been detected in the common Egyptian fruit bat *Rousettus aegyptiacus*, the tree-roosting fruit bat *Eidolon helvum*, and other African bat species [47–51]. Almost all primary infections related to MARV have been linked to humans entering caves inhabited by bats [47]. MARV and EBOV sequences detected in bats are closely related to previously isolated MARV or EBOV sequences and those detected in humans [47,52].

5 Bat reoviruses

The Reoviridae is a family of viruses that can infect a wide range of hosts, from plants to mammals. The genus *Orthoreovirus* is within the Spinareovirinae and contains five virus species: *Pteropine orthoreovirus*; *Avian orthoreovirus*; *Reptilian orthoreovirus*; *Baboon orthoreovirus*; and the type species *Mammalian orthoreovirus* (MRV). Orthoreovirus infection often occurs in animals and humans, but most cases are mild. The first reported bat reovirus, *Pteropine orthoreovirus*, was isolated from the blood of a fruit bat or “flying fox” (*Pteropus poliocephalus*) in New South Wales (Australia) [53]. Thirty years later, a virus similar to *Ptero-*

pine orthoreovirus, which was named Pulau virus, was isolated and identified during the search for natural reservoirs of NiV [54]. Similar viruses were also isolated from the Chinese fruit bat *Rousettus leschenaultia* [55]. Bat-borne orthoreoviruses received increased attention after several orthoviruses (Melaka virus and Kampar virus) were isolated from patients with acute respiratory syndrome in Malaysia in 2007 [56,57], and from three individuals in Hong Kong between 2007 and 2010 [58]. The reoviruses isolated from patients were closely related to those discovered in bats. Epidemiological studies have also indicated that these reoviruses are probably of bat origin. In addition, mammalian orthoreovirus have been isolated from European microbats [59,60], suggesting a high probability of interspecies transmission between animals.

6 Other novel bat viruses

A large number of novel bat viruses have been discovered worldwide and classified into various families, including the Adenoviridae [61,62]; Astroviridae [63,64]; Coronaviridae [65–71]; Circoviridae [72]; Filoviridae [73]; Flaviviridae [74,75]; Hepadnaviridae [76]; Hepeviridae [75,77]; Herpesviridae [78]; Orthomyxoviridae [79,80]; Parvoviridae [81]; Picornaviridae [82]; Papillomaviridae [83]; Paramyxoviridae [41]; and Poxviridae [84]. Most of these novel viruses are distantly related to known animal or human viruses. There exists huge genetic diversity among these novel bat viruses, regardless of whether the genome was RNA or DNA. However, because virus isolation has rarely been successful for most bat viruses, the pathogenesis of these viruses remains unclear. None of the aforementioned viruses has been confirmed to be prevalent in human populations. Although the direct transmission of viruses from wild animals to humans is rare, close attention needs to be paid to the potential threat these novel viruses pose to the public.

It is of interest to note that bats, whether naturally or experimentally infected with viruses, seldom display clinical symptoms. This has been associated with the unique characteristics of the bat immune system. Recently, two bat genomes (*Pteropus alecto* and *Myotis davidii*) have been fully sequenced [85], and an unexpected concentration of positively selected genes were discovered at the DNA damage checkpoint and nuclear factor κB pathway. The DNA damage response plays an important role in host defense and is a known target for virus interaction [86]. This raises the possibility that changes in DNA damage response mechanisms during selection could have influenced the bat immune system. Additionally, several important genes responsible for responding to microbe infections in mammals are lost in both *P. alecto* and *M. davidii*, indicating that immune functions in bats likely differ compared with that in other mammals.

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