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Viruses in bats and potential spillover to animals and humans
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In the last two decades, several high impact zoonotic disease outbreaks have been linked to bat-borne viruses. These include SARS coronavirus, Hendra virus and Nipah virus. In addition, it has been suspected that ebolaviruses and MERS coronavirus are also linked to bats. It is being increasingly accepted that bats are potential reservoirs of a large number of known and unknown viruses, many of which could spillover into animal and human populations. However, our knowledge into basic bat biology and immunology is very limited and we have little understanding of major factors contributing to the risk of bat virus spillover events. Here we provide a brief review of the latest findings in bat viruses and their potential risk of cross-species transmission.

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Introduction
Although there have been significant advances in diagnostics and medical countermeasures during the past century, the risk of cross-species transmission of known and unknown pathogens has emerged as a threat to human and animal populations due to various factors, including industrialization, intensive farming, urbanization, rapid transportation and climate change [1,2]. It is generally accepted that approximately 75% of emerging infectious diseases for humans are zoonoses [1,3,4]. The rate of emergence of novel viruses appears to be increasing as a result of both increased spillover from their natural reservoirs and our improved ability in detection [3].

Among the newly emerged and most deadly zoonotic viruses discovered in the past few decades, bat-borne viruses occupy a greater proportion than viruses from any other mammalian order [5,6,7,8]. Several studies have now concluded that bats are exceptional in their ability to act as natural reservoir of viruses and they are able to harbour more diverse viruses per animal species [6,9]. While the underlying biology for this observation is yet to be uncovered, it is certain that we will witness more disease outbreaks from bat-borne viruses in the years to come.

At the present time, it is impossible to predict the risk of spillover potential for the vast number of viruses or viral sequences which have been detected in bats around the world. But it will be a good start to focus on the viruses in the ‘known unknown’ category, that is new or variant strains of bat viruses related to those which have already spilled over into and caused diseases in animals or humans. Although bats are known to also carry DNA viruses, all of the disease-causing and species-jumping bat-viruses are so far limited to RNA viruses.

In this brief review, we will focus on the major RNA virus families harboured by bats that have demonstrated spill-over and severe disease-causing potential.

Bats as a rich source of emerging viruses
Bats, order Chiroptera, are the only mammals capable of powered flight and are among the most ancient of mammals and underwent extensive speciation for the last 100 million years. There are currently more than 1000 species of bats, making them the second most diverse mammalian group, after rodents, and representing 20% of extant mammalian species [10]. Although the recent surge of interest in bats is mainly driven by their association with many of the most lethal viruses, bats are known for their exceptionally long life span and for being less prone to cancer [8].

Bats are not only rich in species diversity, but also have great variation in their geographical locations, dietary preferences, physiological range of body temperatures, social behaviour and navigation and vision systems [11]. It is therefore important to recognise that such immense diversity makes it difficult to generalize-specific associations relating to bats and viruses to all members of the chiropteran order. In addition, due to the large number of bats around the world and the fact that similar bats can live in different geographical locations and multiple bat species can co-exist in similar ecological habitats, any virus surveillance or virome detection study should not be viewed as a holistic examination of any given systems.
Instead, they are more likely to be a transient snapshot of a specialised system at a given time.

While recognising that there are limitations on current investigations of viruses in bats, we are also optimistic that with the increasing interest and research activities in this field, we will gain a more accurate panoramic view of bats and viruses in the not too distant future. As a matter of fact, the findings accumulated in the last few decades have already pointed towards a few virus families as being both more prevalent in bats and with proven potential for spillover into other animal species [5,12]. The summary below highlights these virus families, followed by other bat viruses which may possess spillover potential and are considered to be important enough to keep on our watch list.

**Coronaviruses**

Coronaviruses were not known to cause severe diseases in humans before the emergence of severe acute respiratory syndrome (SARS) coronavirus (CoV). The SARS outbreak in 2002–2003 remains as one of the most impactful pandemic outbreaks of the 21st century mainly due to the fact that the aetiology was totally unknown during the outbreak, which made accurate diagnosis and effective control impossible [13,14]. The outbreak lasted more than six months with rapid spread of the virus from southern China to more than 30 countries on all major continents, and resulted in more than 8000 human infections and 774 deaths [14]. Multiple international teams spent the next decade hunting for the origin of SARS-CoV and serendipitously found many SARS-CoV related viruses in bats, most abundantly from the genus *Rhinolophus* (horseshoe bats) [15–17]. The most conclusive evidence came from the isolation of a CoV from bats in China which was more than 98% identical in genome sequence to SARS-CoV and capable of using the SARS-CoV receptor, ACE2, on human cells [18*]. While it is not easy to assess the spillover potential of many SARS-CoV related bat CoVs due to unsuccessful attempts to isolate the viruses, it should be noted that a ‘consensus’ virus constructed via reverse genetics pointed to a high probability of human infection [19].

Although a significant amount of attention was focused on SARS-CoV related viruses, the international community was again caught by surprise with the emergence of the Middle East respiratory syndrome (MERS)-CoV in 2012 [20*]. MERS-CoV is genetically quite different from SARS-CoV (Figure 1), despite both viruses belonging to the genus *Betacoronavirus*. As of October 1, 2018, MERS-CoV has infected 2249 people in 27 countries with 35% case fatality [21]. Camels have been identified as important reservoir hosts for MERS-CoV and MERS-CoV related viruses [22,23,24*,25,26,27*], but there is strong evidence that the evolutionary ancestors of these viruses are bats [28,29,30*]. Co-circulation and recombination of CoVs has been implicated as a mechanism that maintains viral diversity and continuous zoonotic transmission [27*,31].

Severe disease outbreaks caused by CoVs related to viruses associated with bats are not limited to humans. In 2016–2017, there was a major outbreak of swine acute diarrhoea syndrome (SADS) in pigslets in multiple southern China farms in a region geographically close to where the SARS outbreak began in 2002 [32**]. The origin of the causative agent, SADS-CoV, was quickly traced back to a bat colony in the vicinity of the pig farms where bat CoV with more than 98% genome sequence identity was detected in *Rhinolophus* spp. bats. SADS-CoV belongs to the genus *Alphacoronavirus* and is genetically most closely related to HKU2, a previously reported bat CoV [32**]. Human coronavirus 229E is in the same genus, but is only distantly related to those bat CoVs. Examination of pig farmers with close contact with sick and dying piglets did not yield evidence of human infection, hence humans may not be susceptible to SADS-CoV. Further study is required to determine the true zoonotic potential of SADS-CoV and closely related bat CoVs.

For unknown reasons, despite of the wide presence of CoVs in bats of different locations and species with relative high viral genome levels, multiple attempts by different international groups to isolate bat CoVs have been largely unsuccessful. The only successful isolation was achieved with SARS-like viruses by direct isolation using Vero E6 cells [18*] or inoculation into the brain of suckling rats [17].

**Paramyxoviruses**

One of the first bat-borne BSL4 agents identified was Hendra virus (HeV) in Australia in 1994 [33*], an emerging pathogen that caused the deaths of 7 people. Additionally, 103 equine and 2 canine cases have been reported [34,35]. In humans the case fatality rate from HeV infection is 57%. All four species of flying fox in Australia (*Pteropus poliocephalus, P. alecto, P. scapulatus* and *P. conspicillatus*) have been found to be seropositive for HeV antibodies and all have detectable virus in their urine with black flying fox (*Pteropus alecto*) being the major reservoir host [36]. A closely related virus, Nipah virus (NiV) emerged in 1998 in Malaysia, which transmitted from bats to humans via pigs as an intermediate and amplifying host [37]. In total, that outbreak resulted in 283 human cases and 109 deaths (39% case fatality) in Malaysia as well as 11 cases and one death in Singaporean abattoir workers [38]. A related, but not identical virus, was responsible for multiple NiV outbreaks in Bangladesh/India [39,40], with the latest outbreak that occurred in 2018 in Kerala and resulted in 19 human infections and 17 deaths [41]. The reservoir hosts of NiV have been identified as the large flying fox (*P. vampyrus*) and small flying fox (*P. hypomelanus*) in Malaysia [42,43]
and the Indian flying fox (P. giganteus) in Bangladesh and India [44,45]. After many years of unsuccessful attempts, NiV was isolated from the Indian flying fox in Bangladesh [46]. The current status of henipavirus transmission during outbreaks is summarised in Figure 2. Apart from HeV and NiV, Cedar virus (CedPV) remains the only other isolated henipavirus species and experimental evidence from animal trials suggests that CedPV is non-pathogenic for humans [47]. Serological evidence of henipavirus infection has been detected in Lyle’s flying fox (Pteropus lylei) populations in Southeast Asia [48], large flying fox in Indonesia [49] and may be endemic among bat populations on the African continent [50–53]. Additionally, a Ghanaian bat henipavirus, Kumasi Virus (KumPV), genome has been sequenced [54**]. Cumulatively, these studies indicate a wide global distribution of henipaviruses.

Menangle virus (MenPV) is a zoonotic paramyxovirus, first identified in a disease outbreak of reproductive disease in pigs in 1997 at a piggery in New South Wales, Australia [55,56]. The virus was also shown to be zoonotic, with 2 piggery workers with high-level exposure developing a serious influenza-like illness and rash during the outbreak. These individuals also developed neutralizing antibodies to MenPV [55]. Bats were hypothesized to be the source of the outbreak and MenPV-neutralizing antibodies were detected in grey-headed flying foxes (Pteropus poliocephalus), black flying foxes (Pteropus alecto) and spectacled flying foxes (Pteropus conspicillatus) [56]. In 2009, MenPV was isolated from a bat roost at Cedar Grove, Australia, where black flying foxes were the predominant species in this colony at the time of sampling [57]. Tioman virus (TioPV) was isolated from urine of the small flying fox (Pteropus hypomelanus) collected from Tioman Island, Malaysia [58]. Due the close relationship of TioPV with the zoonotic MenPV, an experimental challenge of pigs was performed [59] and the trial suggested that pigs could act as an intermediate or amplifying host for TioPV and that oral secretion is a possible means of viral transmission.

The identification of sequences similar to mumps virus (MuV) in bats revealed that a virus that was believed to only infect humans has substantial similarity to a counterpart in bats [54**]. The genetic and functional
relationship between human MuV and bat MuV [60*,61–63] supports the possibility of bats as a reservoir for interspecies transmission.

Aside from MenPV and TioPV, other paramyxoviruses from the genus Rubulavirus have been isolated from or detected in bats without evidence of zoonotic transmission. Porcine rubulavirus (PorPV), the causative agent ‘blue eye’ disease in pigs was first identified in Mexico in 1980 [64] and serological surveillance data [65] suggests bats are likely reservoir of this virus. Mapuera virus (MprPV), a rubulavirus closely related to PorPV [66] that has not been associated with any human disease, was isolated from the salivary glands of a healthy fruit bat (Sturnira lilium) captured in Brazil in 1979 [67].

Tukoko virus (ThkPV) 1, 2 and 3 are rubulaviruses that have been detected and sequenced from Rousettus leschenaultii in China [68], but these viruses were unable to be cultured in the laboratory and the potential of these viruses to cause disease in humans and animals is yet to be ascertained. In 2012, metagenomic analysis from RNA extracted from blood and serum samples of a patient with severe acute febrile illness revealed a novel paramyxovirus [69*] most closely related to ThkPV-3. The novel paramyxovirus was provisionally named Sosuga virus (SosPV) in recognition of its probable geographic origin (South Sudan, Uganda). The patient, a wildlife biologist, developed a severe illness after spending six weeks sampling bats and rodents. Symptoms included fever, malaise, headache, generalized myalgia and arthralgia, neck stiffness, a metallic taste, sore throat and a maculopapular rash that was present later in the infection. The biologist was discharged after two weeks of hospitalization, but considerable sequelae (myalgia, arthralgia, headache, malaise, and fatigue) persisted for several months [69*]. Bat tissues collected during the period just before the onset of symptoms were tested for SosPV, and several Egyptian rousette bats (Rousettus aegyptiacus) were found to be positive. Four additional SosPV-positive samples were found in archived tissues from Egyptian rousette bats collected at other locations in Uganda, suggesting this species could be a potential natural reservoir for this paramyxovirus [70].

Filoviruses
Although it has been known for more than four decades that Ebola and Marburg viruses can cause lethal haemorrhagic diseases in humans, the massive outbreak in west Africa during 2014–16 was unprecedented with more than 11 000 human fatalities [71]. The ongoing Ebola outbreak in the Democratic Republic of Congo is a further indication that more outbreaks in Africa [72].

Currently, there are five distinctive species identified in the genus Ebolavirus, including Bundibugyo (BDBV), Reston (RESTV), Sudan (SUDV), Taï Forest (TAFV) and Zaire (EBOV). Very recently, a sixth species has been proposed, named Bombali virus (BOMV), based on genome sequence detected in free-tailed bats in Sierra Leone (Chaerophon pumilus and Mops condylurus) [73]. Both members of the genus Marburgavirus, Marburg virus (MARV) and Ravn virus (RAVV), have been shown to cause fatal diseases in humans [74,75]. The third genus, Cuevavirus, contains only one species, Lloviu virus (LLOV), whose disease-causing potential in humans is unknown [76,77]. Our group has recently characterized complete coding genome of a new filovirus named...
Mengla virus (MLAV) from *Roussettus* bats in China, which is genetically distinctive from all known filoviruses and most likely represents the prototype of a new filovirus genus (Figure 3), putatively named *Dianlovirus* [78*].

While LLOV, BOMV and MLAV sequences were first discovered in bats, and Marburg viruses have been isolated directly from bats [79*,80], the role of bats as a reservoir for ebolaviruses is still debated mainly due to the lack of direct isolation of ebolaviruses from bats [81]. However, the detection of BOMV seems to strengthen the notion that bats are likely natural reservoirs of ebolaviruses [73].

**Reoviruses**

Reoviruses (respiratory enteric orphan) were not known to be associated with severe human diseases when they were first discovered in the 1950s and about one third of the human population has been exposed to at least one of the mammalian reoviruses (MRVs) [82]. The outbreak of a severe respiratory and enteric disease among different members of a family in Melaka, Malaysia, changed our appreciation of both the diversity and the zoonotic potential of this class of viruses in the genus *Orthoreovirus*, family *Reoviridae* [83**]. Since the discovery of Melaka virus during the 2006 outbreak investigation, at least 15 different strains have been identified, either from human outbreak investigations or bat virome studies [83**], as summarized in Table 1. Serological and molecular detection studies suggest that the prevalence of these viruses could be severely underestimated due to the lack of routine diagnosis in hospitals [96,97].

**Other viruses**

A plethora of known and novel viruses were identified in samples collected and metagenomically screened from straw-coloured fruit bat (*Eidolon helvum*) in Cameroon [98] and *Neoromicia* species in South Africa [99]. These bats were shown to harbor divergent viruses, including members of the families *Astroviridae*, *Circoviridae*, *Parvoceuviridae*, *Partitiviridae*, *Coronaviridae*, *Picobirnaviridae*, *Adenoviridae*, *Herpesviridae*, *Papillomaviridae*, *Pemuicoviridae*, and *Picornaviridae* [98,99]. These recent studies build upon previous work [100–103] to further expand the diversity of the bat virome. Uniquely, the picobirnaviruses identified utilize an alternative genetic code [98].

Similarly, there are many other bat-borne viruses with the potential for zoonotic transmission, but without documented human infection. Rotaviruses and noroviruses, members of the families *Reoviridae* and *Caliciviridae*, respectively, are the major etiologic agents of acute gastroenteritis and several reports have identified rotavirus [98,99,104–106] or norovirus [107,108] sequences in

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**Figure 3**

Genetic relationship of all known filoviruses. The phylogenetic tree was built using MEGA7 using the Neighbor-Joining method with p-distance model under pairwise deletion. The bootstrap value is 1000. Virus abbreviation, full name and accession number are as follows: TAFV, Tai forest virus, NC_014372; BDBV, Bundibugyo virus, NC_014373; EBOV, Ebola virus, NC_002549; SUDV, Sudan virus, NC_006432; RESTV, Reston virus, NC_004161; BOMV, Bombali virus, MF319186; LLOV, Lloviu virus, NC_016144; MARV, Marburg virus, NC_001608; RAVV, Ravn virus, NC_024781; MLAV, Mengla virus, KX371887; XILV, Xilang virus, MG599980; HUJV, Huangjiito virus, MG599981. The two newest members (BOMV and MLAV) are highlighted in red. Genus names are provided on the right with bars indicating the taxonomy boundaries.
different bat species worldwide. The caliciviruses recently discovered in bats were found to be antigenically similar to human noroviruses, again highlighting the potential for cross-species transmission [109].

Influenza virus is known for zoonotic transmission and two novel subtypes were discovered in bats. In 2012, a new influenza virus genomic sequence was identified in frugivorous yellow-shouldered bats (Sturnira lilium) in Guatemala and was designated H17N10 [110]. The following year, a distinct influenza genome, classified as H18N11, was characterized from the flat-faced fruit bat (Artibeus planirostris) in Peru [111]. Although virus isolation was not successful, reverse genetics was used to synthetically generate these viruses [112] and subsequent research highlighted the differences between these viruses and conventional influenza viruses. Identification of these viruses in bats not only expanded the host reservoir of influenza and the genetic diversity of the viruses, but immediately raised the question about zoonotic potential. Studies using synthetic viruses have allowed the identification and characterization of cellular receptors mediating virus attachment and entry, factors important for understanding the tissue tropism and possible zoonotic transmission [112–114].

Hantaviruses are predominantly rodent-borne pathogens and transmission to humans can lead to severe diseases and death. Species of hantaviruses have been identified in bats from Africa and Asia, expanding the potential reservoirs range and genetic diversity of these viruses [115–120]. Hantaan orthohantavirus (HTNV) was isolated from two broadly distributed insectivorous bat species (Eptesicus serotinus and Rhinolophus ferrumequinum) [117]. Evidence of a lethal genotype of Andes orthohantavirus (ANDV), Araraquara orthohantavirus (ARQV), has been documented among several Neotropical bats in Brazil [118,120]. ARQV is one of the most virulent and lethal among all hantaviruses in humans and viral RNA closely related to ARQV was detected in urine of the common vampire bat (Desmodus rotundus) [119]. These studies highlight that bats are probably playing an under appreciated part on the maintenance, circulation, and transmission of hantavirus in nature.

Recently, a group of previous unknown bunyaviruses, including severe fever with thrombocytopenia syndrome (SFTS) virus and Heartland virus (HRTV), emerged during human disease outbreaks [121,122]. Although their animal origins are not known, the most closely related virus has been found in bats in India. In 2010 a novel phlebovirus was isolated from Leschenault’s rousette bat (Rousettus leschenaultii) in western India. The virus was identified by electron microscopy and phylogenetic analysis of the complete genome showed its close relation to SFTSV and HRTV [123].

In contrast to new and emerging viruses where viral pathogenesis and transmission route is unknown, rabies has long been recognized throughout history, due to the characteristic symptoms associated with the disease [124,125]. Infection with lyssaviruses, including rabies virus and Australian bat lyssavirus leads to rabies disease [126]. Although bites and scratches from infected bats occur, there is an effective vaccine and post exposure prophylaxis available for this deadly disease.

### Risk assessment of the ‘known unknowns’

We know that there are several groups of bat viruses that can infect and cause severe diseases in humans, as we have briefly covered in this review. It is also well established that there are a large number of related viruses circulating in bats in different parts of the globe, but as of yet we are unable to accurately predict which of these

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| Table 1 |
|-----------------------------------------------|
| **Summary of known pteropine orthoreoviruses (PRVs)** |
| **PRV Isolate** | **Alternative name** | **Year of isolation** | **Host** | **Country of Origin** | **Reference** |
|-----------------|----------------------|-----------------------|----------|-----------------------|--------------|
| PRV1NB          | Nelson Bay Virus     | 1968                  | Bat (Pteropus poliocephalus) | Australia       | [84]         |
| PRV2P           | Pulau Virus          | 1999                  | Bat (Pteropus hypomelanus)   | Malaysia         | [85]         |
| PRV3M           | Melaka Virus         | 2006                  | Human                            | Malaysia         | [83**]       |
| PRV4K           | Kampar Virus         | 2006                  | Human                            | Malaysia         | [88]         |
| PRV5HK          | Xi River virus       | 2007                  | Human                            | Indonesia        | [67]         |
| PRV6XR          | Sikamat Virus        | 2010                  | Human                            | Malaysia         | [89]         |
| PRV7S           | HK46886/09           | 2009                  | Human                            | Indonesia        | [90]         |
| PRV9HK          | HK50842/10           | 2010                  | Human                            | Indonesia        | [90]         |
| PRV10M          | Miyazaki-Bali 2007   | 2007                  | Human                            | Indonesia        | [91]         |
| PRV11C          | Cangyuan virus       | 2012                  | Bat (Roussettus leschenaultii)   | China            | [92]         |
| PRV12I          | Indonesia/2010       | 2010                  | Bat (Pteropus vampyrus)          | Indonesia        | [93]         |
| PRV13P          | Samal-24             | 2013                  | Bat (Eonycteris spelaea)         | Philippines      | [94]         |
| PRV14P          | Talikud-80           | 2013                  | Bat (Roussettus amplexicaudatus)  | Philippines      | [94]         |
| PRV15G          | Garut-69             | 2017                  | Bat (Pteropus vampyrus)          | Indonesia        | [95]         |

**a** PRV numbering nomenclature is based on the temporal sequence of isolation or detection and/or publication.
viruses are capable of spillover and whether they will cause diseases in humans. We view these viruses as the ‘known unknowns’. Among the four families of viruses discussed in this review, each has a different combination of characteristics.

In terms of frequency, the reoviruses seem to be the most permissive to spillover, especially in Asia. However, to date we have only experienced severe, but not lethal, infections in humans. On the other hand, filoviruses and henipaviruses are far the more deadly but the frequency of spillover is relatively low [7,12]. Rabies virus is highly lethal and responsible for a large number of human deaths. But the direct spillover from bats to humans is limited. In contrast, the known genetic diversity of CoVs in bats is much greater than any of the other bat zoonotic viruses. CoVs contain the largest genomes of all known RNA viruses, and hence are naturally exposed to a higher chance of genetic mutation per genome. To prevent frequent ‘lethal mutations’, CoVs have evolved to contain an exoribonuclease which increases the fidelity of RNA genome replication [127,128]. However, the large positive RNA genomes of CoVs are highly prone to gross genetic changes via recombination, which is elegantly illustrated by two recent studies, one on SARS-like viruses [129*] and another on the discovery of a recombinant CoV containing a reovirus P10 gene sequence [130*,131]. The true rate of CoV spillover into humans and livestock animals may be greatly underestimated as these occurrences do not always cause severe or lethal disease, demonstrated by serological surveillance. Spillover and zoonotic transmission of CoVs is not limited to bat CoVs, rather increasing evidence suggests the emergence of new CoV strains and the mutation of existing strains resulting in new disease syndromes in both animals and humans [132,133].

One of the challenging scientific questions is why many of the bat-borne zoonotic viruses are so lethal when they spill over into human and/or livestock animal populations. Up until now, our knowledge was very limited in addressing this question due to lack of research tools to conduct comparative immunology and pathogenesis studies in bats. Several recent studies, however, start to reveal that bats may have evolved a more balanced innate defence system. On one hand, bats have elevated level of certain defence genes or pathways from type I interferon [134] to apoptosis [135], at the same time bats exhibit more immune tolerance in different pathways, from inflammation [136], STING signalling [137] to NK cell activation [138]. However, it should be cautioned that these are very early and preliminary studies, many of them based on genomics and bioinformatics analysis only, more in-depth functional studies are required to get a better understanding of the asymptomatic infection of bats by viruses highly lethal in other mammals.

Conclusion
The importance of bats as a source of emerging viruses has been proven from numerous studies in the last two decades. While most of the investigation is triggered by zoonotic spillover of bat viruses, the impact of spillover into livestock animals should not be underestimated as shown by the SADS-CoV outbreak. From the great genetic diversity and wide geographical locations of the various bat viruses detected so far, it is almost certain that we will see more and more disease outbreaks caused by bat viruses. Among the ‘known unknowns’, bat coronaviruses may be a more likely cause of future spillover into both human and livestock populations due to their greater genetic diversity already known in bats around the world, their large positive strand RNA genome size with a high rate of recombination, and proven spillover events in both human and animals. We are still at an infancy stage in terms of understanding bat biology in the context of how some of the most lethal viruses can peacefully co-exist with bats, but most recent research findings suggest the key but not in other mammals.

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