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Bats and their virome: an important source of emerging viruses capable of infecting humans

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Bats are being increasingly recognized as an important reservoir of zoonotic viruses of different families, including SARS coronavirus, Nipah virus, Hendra virus and Ebola virus. Several recent studies hypothesized that bats, an ancient group of flying mammals, are the major reservoir of several important RNA virus families from which other mammalian viruses of livestock and humans were derived. Although this hypothesis needs further investigation, the premise that bats carry a large number of viruses is commonly accepted. The question of whether bats have unique biological features making them ideal reservoir hosts has been the subject of several recent reviews. In this review, we will focus on the public health implications of bat derived zoonotic viral disease outbreaks, examine the drivers and risk factors of past disease outbreaks and outline research directions for better control of future disease events.

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Introduction

Approximately 75% of emerging infectious diseases are zoonoses [1,2]. The rate of emergence of zoonotic viruses appears to be increasing and/or our ability to detect new viruses is improving. Viruses are well adapted to their reservoir hosts and therefore exhibit stability within their host's cellular and ecological environments and display little or no clinical disease in these species. However, when a virus jumps the species barrier and spills over into humans, the effects can be devastating. Only when these viruses from wildlife spillover to humans or their domesticated animals and cause mortalities, does this become a significant concern for public health. High mortality rates often characterize these spillover events as do high economic losses. This is particularly true for the bat borne viruses that have emerged in the last 20 years such as

Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Nipah virus (NiV) Hendra virus (HeV) and Ebola virus (EBOV). International travel has contributed to the transmission of many infectious diseases and the bat borne zoonotic viruses are no exception with the most notable being the transmission of SARS-CoV from the key port in Hong Kong to Canada, the Americas, Europe, Asia and Australasia resulting in 8422 cases with 916 deaths (10.9% case fatality) [3].

Bats, order Chiroptera, comprise greater than 20% of living mammalian species with more than 1100 species across 17 families [4]. They are among the most ancient of mammals, their extensive speciation occurred before development of most modern mammals, and they are the only mammals capable of powered flight. Bats in general are also very long-lived and more widely dispersed globally than other mammals; they play vital roles as pollinators of hundreds of species of plants and trees and in the control of arthropod populations. More recently, resurgence in interest in bat biology and ecology has been sparked by their recognition as the known reservoir hosts of some of the most deadly viral zoonoses [5], to which they appear resistant to any pathogenic effects. Whether bats are unique or special as a reservoir of viruses has been the subject of several recent publications [6,7] and will not be covered in this review. This review will focus on the ecology, pathogen–host interface and public health considerations of selected bat zoonotic viruses.

Key examples of bat zoonotic viruses

Hendra virus (HeV)

HeV first emerged in 1994 in an outbreak of respiratory disease that infected 20 horses and two humans, resulting in the death of all horses and one of the humans [8,9]. There have been a total of 39 spillover events identified resulting in the infection of 78 horses, one dog and seven humans. In humans the case fatality rate from HeV infection is 57%. The four species of flying fox, *Pteropus poliocephalus*, *P. alecto*, *P. scapulatus* and *P. conspicillatus* have been found to be seropositive for HeV antibodies [10] and all have detectable virus in their urine [11,12]. All human cases of HeV infection have been associated with veterinarians and the continual outbreaks have resulted in many veterinarians leaving the equine field due to fears of HeV infection and legal liability [13].

Nipah virus (NiV)

There have been two clusters of Nipah virus outbreaks detected since the end of the 1990s, one in Malaysia/

Singapore and the other in Bangladesh/India. NiV first emerged in Malaysia, causing an outbreak of neurological and respiratory disease affecting pigs between September 1998 and June 1999. Transmission from pigs to humans resulted in 283 human cases and 109 deaths (39% case fatality) in Malaysia and 11 cases and one death in Singaporean abattoir workers [14,15]. The outbreak was controlled by the slaughtering of over 1.1 million pigs [16]. The reservoir hosts of NiV have been identified as *Pteropus vampyrus* and *Pteropus hypomenalus* in Malaysia [17,18,19^{*}] and *P. giganteus* in Bangladesh and India [20,21].

Since 2001, outbreaks of NiV in Bangladesh and India have occurred almost on an annual basis with a total of 302 cases and 210 human deaths (69.5% case fatality) [22,23]. In Bangladesh and India, NiV shedding in *P. giganteus* bats appears to result in direct transmission to humans via consumption of raw date palm sap contaminated with bat excreta (saliva, urine, faeces) without transmission through an intermediate host [24^{**},25]. Person to person transmission has also been observed [26,27].

Severe Acute Respiratory Syndrome coronavirus (SARS-CoV)

In 2003, a global outbreak of SARS started in southern China and Hong Kong leading to 8422 cases and 916 human deaths (10.9% case fatality) worldwide [28]. For the transmission of SARS-CoV to humans, the virus required rapid adaptation through the intermediary host which was thought to be the palm civet (*Paguma* sp.) where adaptation allowed for transmission of the sufficiently fit virus to humans [29^{**}]. The cave dwelling fruit bat *Rousettus leschenaultii* was identified as the reservoir host of SARS-like coronaviruses [29^{**}]. The SARS-CoV outbreak was estimated to have cost \$US54 billion globally [30].

Ebola virus (EBOV)

The transmission of EBOV to humans has usually occurred through the capture and slaughtering of animals, commonly non-human primates, for 'bush meat' [31]. The fruit bats *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata* are possible reservoirs for EBOV in Africa based on serological surveys [32^{**}]. The initial outbreaks of EBOV in 1976 in Sudan and Zaire were exacerbated by the reuse of contaminated needles [33,34]. Person to person transmission occurs through contact with bodily fluids (blood, semen, organs, urine, faeces and secretions) [35] including contact with cadavers [36].

Initially identified in imported macaques in the USA, Ebola Reston has recently emerged in pigs in the Philippines and poses a concern for Public Health and agriculture. Of particular significance was the co-infection of the pigs with porcine reproductive and respiratory syndrome virus and porcine circovirus type 2. Serological

studies identified six people that had seroconverted to Ebola Reston virus, all of which has contact with sick pigs [37]. Importantly, experimental infection with Ebola Reston virus found that the disease was asymptomatic in pigs despite shedding, indicating a risk for farm and abattoir workers [38]. Antibodies to Ebola Reston virus were detected in *Rousettus amplexicaudatus* bats implicating this bat as a potential reservoir host [39].

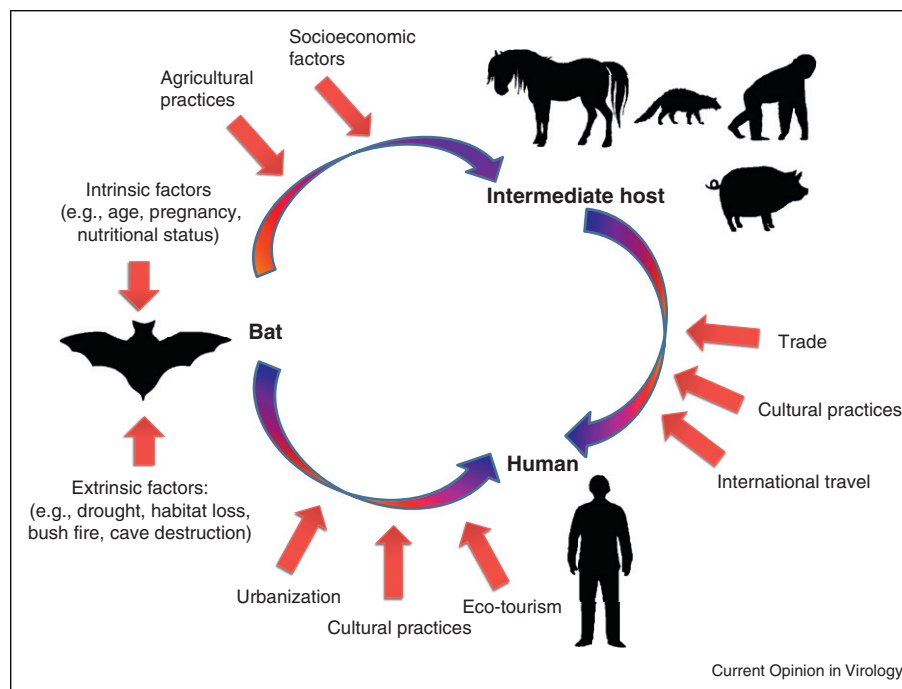
In addition to the 'high impact' bat zoonotic viruses discussed above, there are other bat viruses which have caused zoonotic infections. See Table 1 for a summary list of major bat zoonotic viruses recently emerged.

Understanding the ecology of disease emergence

There are many potential drivers that can contribute to a spillover of zoonotic bat-borne disease (Table 1 and Figure 1). These factors can be extrinsic and/or intrinsic. Extrinsic factors such as environmental and anthropogenic stressors can have an effect on the ecology of disease in bats. Environmental stressors such as climatic events (typhoons/cyclones and droughts) that destroy habitat and food resources have been hypothesized to have an impact on the health of bats [40–43,44^{*}]. In addition, human activities are selecting for some species of bats that are synanthropic, and so are benefiting from living close to humans, thereby increasing their numbers and the risk of transmission of disease to humans [45]. Human activities are artificially increasing animal densities by changing the land use and this is increasing the contact between humans, domesticated animals and bats [46]. In the cases of Hendra virus, Nipah virus and Menangle virus, domesticated animals are the amplifying hosts of these zoonotic viruses [15,47,48]. Habitat change such as deforestation force changes in roosting sites and can lead to alterations in the population density and the migratory patterns of bats. These anthropogenic activities may be impacting our ecosystem in such a way that the equilibrium is disturbed and spillover of zoonotic viruses readily occur [49–51].

In the case of the NiV outbreak in Malaysia, the drivers of the outbreak were primarily agricultural intensification and more specifically the co-location of pig farms and fruit orchards. It is believed that the fruiting trees overhanging the intensive pig farms attracted flying foxes, leading to NiV spillover into pigs [52]. It has been hypothesized that the Nipah virus outbreak in pigs was contributed by the El Niño Southern Oscillation induced drought and subsequent forest fires in Indonesia that produced a smoke haze that led to the migration of flying foxes into Malaysia and the subsequent spillover of NiV into pigs [52]. However, this hypothesis was refuted by a later study which suggested that there were multiple introductions of NiV into the piggery. It was thought that repeated introductions of NiV allowed for viral persistence to be established

Figure 1



Examples of drivers responsible for zoonotic virus spillover from bats.

within the pig population which in turn resulted in transmission of NiV to humans [53]. NiV underwent a host shift from fruit bats into pigs that allowed for high levels of virus to be shed and persist within a new host. Management practices of relocating pigs to grower farms further spread the virus. Trade allowed for further NiV transmission with pigs being transported to Singapore for processing increasing the spread of the outbreak [14].

The drivers for transmission of NiV in Bangladesh differed to those in Malaysia. In Bangladesh, cultural practices of consumption and trade of date palm sap have allowed for the transmission of NiV from bats to humans [24,25]. Traditional social practices of family members caring for the sick in the absence of barrier nursing have resulted in person-to-person transmission further contributing to outbreaks of disease [26,27].

Similarly, cultural traditions of eating wild animal meat or 'bush meat' in Africa and Asia have led to outbreaks of EBOV and SARS-CoV. In the case of EBOV, the transmission has been further exacerbated by the lack of barrier nursing and the use of traditional burial practices where mourners make contact with the deceased [36]. Desire for wild animal meat including bats, and trade in live wet markets have allowed susceptible animals to come into contact with bats enabling the subsequent transmission of SARS-CoV into humans [54,55]. Once established, person-to-person transmission occurred and

the virus was widely spread by international travellers [56]. Importantly, international collaboration allowed for the aetiology of the outbreak to be rapidly determined. This in turn allowed for the development of diagnostic assays for the detection of the virus and greatly assisted in the control of the outbreak [3]. Recently, a novel coronavirus isolated from a Saudi male patient suffering pneumonia and renal failure was determined to be most similar to bat coronaviruses through an international collaboration [57,58*]. Following the posting on Promed of this case [57], another coronavirus with 99.5% similarity to the virus was identified as the causative agent of a Saudi man from Qatar (and hospitalized in London) suffering from a severe respiratory illness [59]. This allowed the development of real-time molecular assays for the rapid detection of these viruses [60]. More recently, another Saudi man has been diagnosed with a similar coronavirus infection [61].

Overall, ecology-based management of drivers that can lead to spillover are likely to be more effective than movement or culling, as they have the potential to reduce disease susceptibility in the reservoir host and opportunities for transmission [42,44].

Understanding the virus–bat interface

Our understanding of virus–host interactions is in its infancy. The virus–bat interface is impacted by the extrinsic factors mentioned above, as well as viral and

Table 1

Comparison of drivers and risk factors for selective emerging bat zoonotic viruses

Virus	Drivers	Risk factors/modes of transmission	References
SARS-CoV	Economic growth Desire for game meat Live wild animal trading in wet markets International travel	Slaughtering Social/cultural practices Farming of wild animals Laboratory acquired infection	[29**,54,55,93]
Ebola virus	Desire for game meat (Bush meat) Live wild animal trading Burial practices	Slaughtering/hunters Social/cultural Practices Poor health care practices	[31]
Marburg virus	Infected monkeys used for research Mining Tourism	Laboratory acquired infection Caves (eco-tourism) Mining	[84,94–96]
Hendra virus	Population growth/urbanization/ human encroachment/ synanthrophy Climate change Starvation Reproductive stress	Inadequate PPE for veterinarians Intermit contact with horses (cuts, abrasions, respiratory secretions) For example performing necropies	[13,46,62]
Nipah virus (Bangladesh)	Date palm juice Cultural tradition	Drinking date palm juice Caring for infected patients	[26,27,90,97,98]
Nipah virus (Malaysia)	Agricultural intensification (dual land use) Encroachment into forested areas Movement of pigs to grower piggeries within Malaysia Food processing in Singapore Trade Habitat destruction Stress	Piggery workers (aerosols, husbandry practices) Abattoir workers (slaughtering)	[53,99,100]
Reoviruses (Melaka virus and related viruses)	Urbanization Tourism	Close proximity to bats Eco-tourism	[101,102]
Menangle virus	Agricultural practices (transportation of pigs within farm) Movement of pigs to grower piggeries Close proximity to flying fox colony	Piggery workers (husbandry practices – birthing and necropies without PPE)	[47]
Lyssaviruses for example Rabies, Australian bat lyssavirus (ABLV), European bat lyssaviruses (EBLV) 1 and 2, Lagos bat virus, Duvenhage virus	Urbanization Deforestation Synanthrophy	Bat carers Cohabitation with bats in houses	[42,44*]

host factors (intrinsic factors). There are multiple intrinsic factors of the reservoir host such as age, body condition, reproductive status, sex and social status that are impacted by stress. For instance, stresses due to starvation and the breeding season for males may play an important role in the epidemiology of disease as stress caused by these factors may dampen the immune response making individuals more susceptible to infection [62]. In the case of EBOV, it is thought that starvation leads to fruit bats and primates coming into close proximity during their quest for food, facilitating spillover [63]. Transmission of viruses could also occur following changes in the hierarchy of the colony that lead to fighting for dominance, and during courtship and mating via grooming and biting [7]. Seasonal periods when juveniles have waning

maternal antibody and are therefore susceptible to virus infection have been associated with increased transmission of Marburg virus to humans [64**] and have been thought to have a role in increasing the incidence of transmission within bat colonies for HeV as well as Marburg virus [46,62,64]. Bats live on average 3.5 times longer than a mammal of similar size [65], hence longevity in bats promotes persistence of viruses in the reservoir host, while the ability to fly allows long-distance dispersal of the infectious agent. Aerosols, direct contact and arthropods could also serve as vectors for transmission within the colony or to other species.

Little is known about the diversity of viruses, the amount of virus present, the mechanisms of shedding,

the incidence of supershedders or the contact rates between infectious and susceptible individuals. From metagenomic analyses, bats harbour a range of viruses and there is a possibility of multiple viral infections in bats spilling over [66–68]. Notably, all of the zoonotic viruses of bat origin so far identified are RNA viruses. Many of these highly pathogenic viruses display a broad cell tropism, being able to infect a wide range of cells and hosts (HeV, NiV, EBOV, SARS-CoV) [69–72]. Viruses such as HeV, lyssaviruses and NiV show high genome conservation within their bat hosts, suggesting that they are under strong selective constraints [11^{*},73–76].

Public health considerations: prevention and control strategies

Understanding the ecology of bat-borne viral pathogens and identifying the triggers of an outbreak will assist in the control or reduction of emerging zoonotic disease outbreaks. By understanding the mechanisms of emergence, outbreak management plans can be developed and risk mitigation processes can be implemented. Once identified, risk reduction strategies can be implemented through education of the general public, doctors, veterinarians and policy makers [77]. Measures such as the wearing of appropriate protective equipment (PPE) when caring for patients or animals and restriction on the sale and consumption of game meat would reduce the risks of transmission of bat-borne viruses.

Following outbreaks of disease, public health measures implemented have included enhanced surveillance and increased infection control, whether it is in hospitals in the case of SARS-CoV, EBOV and NiV, or during veterinary procedures in the case of HeV. Quarantine and contact tracing to limit the spread of viruses have also been implemented in outbreaks [16,78,79^{**},80–84]. A communication strategy is implemented to inform the public aims to reduce further spread by avoidance of risky activities or alteration of activities. For example, following the recognition of SARS, response teams were formed and communication to the public was instigated including global alerts from the World Health Organization [85].

Implementation of prevention and control measures can be carried out at many different levels. At the farming level, changing agricultural practices by the creation of buffers between fruiting trees and domesticated animals would significantly reduce the transmission for HeV and NiV, which is believed to have already played an important role in preventing further NiV outbreaks in Malaysia [86,87]. The introduction of biocontainment measures within piggeries, including surveillance of pigs being transferred between farms and sent to abattoirs, is another effective approach which can be applied at the farming and trade level [87–89]. Since some of these zoonotic agents involve an intermediate host of livestock importance, it is highly important that veterinarians wear appropriate PPE when

performing procedures on animals to minimize the risk of transmission of zoonotic diseases.

In addition to the above general strategies, some disease-specific prevention and control measures can also be applied. In Bangladesh, the installation of barriers on the date palms that prevent the bats from accessing the collection vessels is a simple strategy currently being investigated to control transmission of NiV. This strategy also improves the quality of sap and therefore results in a higher price [90,91,92^{**}]. For prevention of HeV infection in humans, a One Health approach is being adopted. This involved the development of a recombinant protein-based vaccination program for horses in high-risk areas. The vaccination aims to achieve two purposes: prevent horses from HeV infection and, more importantly, block the horse-to-human transmission. With the recent release of a vaccine against HeV in early November 2012, it will be interesting to see whether this One Health strategy is effective in interrupting the zoonotic transmission cycle of HeV.

Strategies for the development of surveillance for new and emerging diseases and the management of bats need to be developed. With increased interaction between humans and their domesticated animals and bats, increasing rates of infections will continue to occur. In the past, there has been passive surveillance on dead animals, and it is time to form an international consortium for active surveillance of different bat populations to detect potential zoonotic agents as well as unknown viruses of low pathogenicity that could combine with other viruses to be pathogenic [42]. The use of new technologies such as high throughput sequencing and multiplex serological tests should be an integral part of this effort to increase our ability for pre-emergence monitoring of potential zoonotic pathogens.

Future directions

With human activity increasingly overlapping the habitats of bats, there is no doubt that zoonotic viruses will continue to emerge from these species. In order to help predict and prevent the emergence of viruses, we need a greater understanding of the infection dynamics within their hosts and to understand the impact of human changes to the environment on the potential for virus spillover. A fully integrated One Health approach with international scientists, ecologists, veterinarians, health professionals, social scientists and politicians working together is required to minimize the impact of bat borne zoonotic diseases. It is critical that we are able to coexist with bats as these unique creatures are vital to our ecosystem.

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