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Emerging henipaviruses and flying foxes – Conservation and management perspectives

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ABSTRACT

Wildlife populations are affected by a series of emerging diseases, some of which pose a significant threat to their conservation. They can also be reservoirs of pathogens that threaten domestic animal and human health. In this paper, we review the ecology of two viruses that have caused significant disease in domestic animals and humans and are carried by wild fruit bats in Asia and Australia. The first, Hendra virus, has caused disease in horses and/or humans in Australia every five years since it first emerged in 1994. Nipah virus has caused a major outbreak of disease in pigs and humans in Malaysia in the late 1990s and has also caused human mortalities in Bangladesh annually since 2001. Increased knowledge of fruit bat population dynamics and disease ecology will help improve our understanding of processes driving the emergence of diseases from bats. For this, a trans-disciplinary approach is required to develop appropriate host management strategies that both maximise the conservation of bat populations as well as minimise the risk of disease outbreaks in domestic animals and humans.

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1. Henipaviruses – emerging viruses with Pteropus bat reservoirs

Outbreaks of previously unknown viral diseases with wildlife reservoir hosts are part of an important phenomenon for public health and conservation – disease emergence. Emerging infectious diseases (EIDs) are defined as diseases that have recently increased in incidence, impact or geographic range; have recently moved into new populations; or are caused by recently evolved pathogens (Daszak et al., 2000; Lederberg et al., 1992; Morse, 2004). Like most infectious diseases, EIDs represent a complex interplay between host, environment and pathogen, and their emergence is usually multifactorial. Morse (2004) categorised factors that underlie this process and cited international travel, human population movement

(due to war, economic migration, etc.), agricultural and food-processing changes, pathogen or host invasion into new regions and human encroachment into wildlife habitat (Daszak et al., 2000; Lederberg et al., 1992; Morse, 2004).

Emerging diseases and wildlife interact in two major ways: firstly, wildlife are reservoirs of pathogens that threaten domestic animal and human health (like Nipah and Hendra virus); secondly, wildlife populations are themselves affected by a series of emerging wildlife diseases, some of which pose a substantial threat to the conservation of biodiversity (Daszak et al., 2000). This has led to increasing realisation of the interconnectedness of ecosystem and human health leading some to propose that emerging diseases exist within a finely balanced host-pathogen continuum between wildlife, domestic animal and human populations (Daszak

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et al., 2000). Anthropogenic environmental changes can therefore have significant consequences for conservation as well as public health through promoting the emergence of both zoonotic and wildlife diseases. The connections suggest that a transdisciplinary approach is needed to tackle the challenge of emerging diseases and conservation. This includes consideration of medical, environmental, economic and socio-political factors (Daszak, 2005). These connections also highlight the need to consider diseases in wildlife populations when planning their conservation, and conversely the need to consider the conservation of wildlife populations when planning disease management strategies (Macdonald and Sillero-Zubiri, 2004).

Recent analyses demonstrate that around 75% of EIDs affecting humans are caused by zoonotic pathogens (those transmissible between animals and humans) (Taylor and Woolhouse, 2000). In some cases, reservoir hosts of these zoonoses are domestic animals, but many of the most significant EIDs of recent times have emerged from wildlife reservoirs (e.g. henipaviruses, SARS, hantaviruses, Ebola virus, West Nile virus, Lyme disease) (Daszak et al., 2000; Hoar et al., 1998; Li et al., 2005). In this paper, we discuss the emergence of a genus of zoonotic paramyxoviruses (*Henipavirus*) from fruit bats (*Pteropus* spp.). With over 50 species, the genus *Pteropus* is the largest genus of the Old World fruit bats (Family Pteropodidae) (Fig. 1). The genus *Henipavirus* includes two viruses (Hendra virus, Nipah virus) which emerged during the 1990s causing death in domestic animals (horses and pigs respectively) and severe disease with high case fatality rates in humans. Their emergence, and the recent discovery of other viruses with *Pteropus* spp. bats reservoir hosts has caused great interest in the medical field (Field et al., 2001; Hyatt et al., 2004). However, little is known of the effect of henipaviruses in their natural reservoir or of their ecology and host-pathogen dynamics.

In this paper, we review the ecology, epidemiology and biology of henipaviruses as an example of the interaction between disease agents, wildlife, domestic animals and humans. This interaction has important conservation implications because the processes driving the spillover of

these infectious agents from flying foxes are some of the key threats for flying fox populations. These threats include hunting, roost disturbance and habitat loss or alteration (Duncan et al., 1999; Mickleburgh et al., 1992; Pierson and Rainey, 1992).

2. Emerging paramyxoviruses and wild mammals

The *Paramyxoviridae* family contains a series of viruses that infect wild mammals (see Table 1 and Fig. 2).

3. Emerging infectious diseases associated with bats

Historically, a wide range of viral infections (including flaviviruses, alphaviruses, rhabdoviruses, arenaviruses, reoviruses, and paramyxoviruses) has been identified in bats (Sulkin and Allen, 1974). More recently, bats have been associated with a number of emerging zoonotic viruses (Hoar et al., 1998) (see Table 2).

The identification of bats as reservoirs for Nipah virus, Hendra virus, SARS-like coronaviruses and Ebola virus has led some authors to propose that bats are unique in their response to viral infection and are able to sustain viral infections without disease (Dobson, 2005; Sulkin and Allen, 1974). However, many other small mammals act as reservoirs for viruses without evidence of disease, and recent analysis of a database on all EIDs of humans suggests that bats (which represent as much as a quarter of all mammal species) do not harbour a disproportionate number of the known emerging zoonotic viruses (Dobson, 2005; Woolhouse and Gowtage-Sequeria, 2005). The ecology and biology of these viruses in bat populations is not well known, due, in part, to difficulties associated with disease investigations of wildlife populations. In particular, for *Pteropus* spp., there is a lack of information on wildlife population biology and basic parameters such as population size, age and sex structure, rates of immigration, emigration, birth and mortality are frequently unknown. Additional constraints arise due to invalid or inadequate diag-

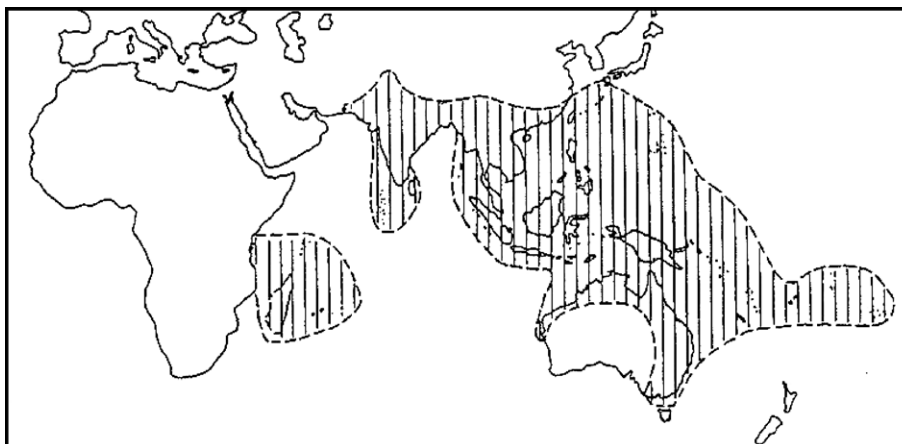


Fig. 1 – World distribution of flying foxes (Genus *Pteropus*) (from Hall and Richards (2000)). In this paper the term ‘flying fox’ refers only to members of the genus *Pteropus*, although other genera, e.g. *Acerodon*, are also considered flying foxes by some authors.

Table 1 – Paramyxoviruses known to infect wild mammals

Genus	Species	Disease outbreaks or putative host	Reference
Morbillivirus	Canine distemper virus	Mass mortality in lion populations in the Serengeti	Roelke-Parker et al. (1996)
Morbillivirus	Measles virus	Disease outbreak in mountain gorillas	Hastings et al. (1991)
Morbillivirus	Rinderpest	Pandemic of African Artiodactyla 1889–1897	Scott (1964)
Morbillivirus	Phocine distemper virus	Disease outbreak in seals	Osterhaus et al. (1990)
Morbillivirus	Cetacean morbilliviruses	Disease outbreaks in dolphins	Taubenberger et al. (1996)
Rubulavirus	Mapuera virus	Isolated from bat species (<i>Sturnira lilium</i>) in Brazil	Henderson et al. (1995)
Rubulavirus	Menangle virus	Severe reproductive disease in intensively farmed pigs in Australia	Philbey et al. (1998)
Rubulavirus	Tioman virus	Isolated from flying foxes in Malaysia	Chua et al. (2001)
Henipavirus	Hendra virus	Sporadically caused disease in horses and humans in Australia	Murray et al. (1995)
Henipavirus	Nipah virus	Major epidemic in pigs and humans in Malaysia	Chua et al. (2000) and Nor et al. (2000)
Unclassified	Tupaia paramyxovirus	Isolated from an apparently healthy tree shrew in Thailand	Tidona et al. (1999)
Unclassified	Pulau virus	Isolated from flying foxes in Malaysia	Chua et al. (2001)
Unclassified	bat parainfluenza virus	Isolated from Old World fruit bat <i>Rousettus leschenaultia</i> in India	Pavri et al. (1971)
Unclassified	Mossman virus	Isolated from Cape York Rats <i>Rattus leucopus</i> in Australia	Campbell et al. (1977)
Unclassified	J virus	Isolated from house mice and brown rats in Australia	Jun et al. (1977)

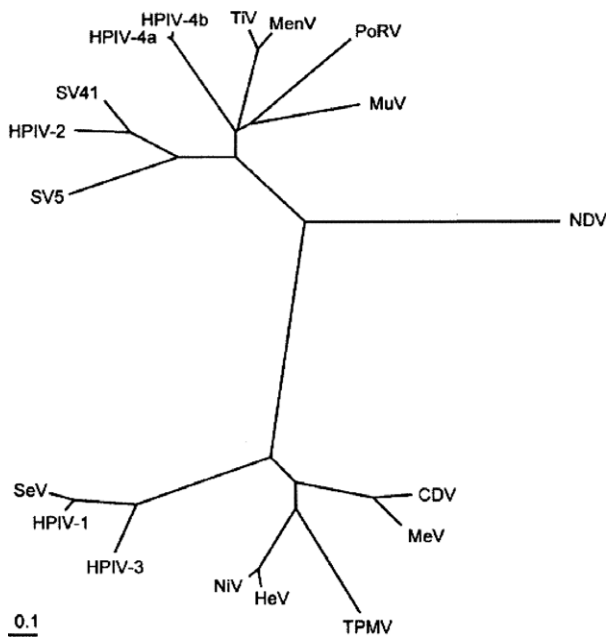


Fig. 2 – A phylogenetic representation of the family Paramyxoviridae (from Chua et al., 2002). A phylogenetic tree based on the deduced amino acid sequences of the matrix protein of members of the family Paramyxoviridae. Branch lengths represent relative evolutionary distances. NDV, Newcastle disease; CDV, canine distemper virus; MeV, measles virus; TPMV, Tupaia Paramyxovirus; HeV, Hendra virus; NiV, Nipah virus; HPIV3, human parainfluenza virus 3; HPIV1, human parainfluenza virus 1; SeV, Sendai virus; SV5, Simian virus 5; HPIV2, human parainfluenza virus 2; SV41, Simian virus 41; HPIV4a, human parainfluenza virus 4a; HPIV4b, human parainfluenza virus 4b; TiV, Tioman virus; MenV, Menangle virus; PoRV, porcine rubulavirus; MuV, mumps virus.

4. Population ecology and disease ecology in flying foxes

Of 51 flying fox species assessed, over half (27) are classified as threatened and thus of significant conservation concern (Mickleburgh et al., 1992). Although the other 24 species are considered to be at lower risk, there is evidence of population declines in many species (Pierson and Rainey, 1992). In south-east Asia, where most flying fox species occur, there is widespread hunting of native fauna, a high rate of habitat loss, and few if any formal bat conservation programs (Mickleburgh et al., 1992). In Malaysia, the Island flying fox (*Pteropus hypomelanus*) and the Malayan flying fox (*Pteropus vampyrus*) – the reservoirs of Nipah virus there – are protected under the Wildlife Protection Act of 1972. However, commercially licensed hunting is authorised by the Perhilitan (Wildlife Department of Malaysia), and it is believed that illegal hunting also occurs. Flying foxes are generally regarded as agricultural pests by fruit orchard owners, and are also hunted for sport and for food in Malaysia. In some cases, eating bats is thought to bring medicinal benefit as a treatment for asthma. Following the emergence of Nipah virus, there have been no large-scale attempts to exterminate the local populations of flying foxes, however hunting continues year-round. Populations of *P. vampyrus* have declined over the past few decades, and the Perhilitan (Wildlife Department of Malaysia) is currently re-assessing the level of protection afforded to this species under the Wildlife Protection Act (Mislih pers. comm.; Mickleburgh et al., 2002; Mohd-Azlan et al., 2001).

Bats are the only mammals capable of sustained flight and many flying foxes travel hundreds of kilometres in a matter of days (Eby, 1991; Hall and Richards, 2000). This may have significant implications for disease spread and also suggests that populations of pathogens carried by flying foxes are likely to be relatively homogenous across large regions. Studies of flying foxes using satellite telemetry have shown individual flying foxes to be capable of travelling over 2000 km per year (Daszak et al., 2006; Tidemann and Nelson, 2004) and traversing significant bodies of open sea such as Torres Strait between Australia and New Guinea, and the Strait of Malacca between

nostic tests, statutory protection afforded by these bats' species conservation status, and public opposition to research on the wildlife species involved.

Table 2 – Emerging zoonotic diseases associated with bats

Virus	Host	Location	Reference
Hantaan virus	Common serotine bat (<i>Eptesicus serotinus</i>) horseshoe bat (<i>Rhinolophus ferrumequinum</i>)	Korea	Hoar et al. (1998)
Rift Valley fever virus	<i>Micropteropus pusillus</i> and <i>Hipposideros albae</i>	Republic of Guinea	Hoar et al. (1998)
Yellow fever	Old World fruit bat <i>Epomophorus</i> sp.	Ethiopia	Hoar et al. (1998)
Venezuelan equine encephalitis virus	Bat species	Guatemala	Hoar et al. (1998)
St. Louis encephalitis virus	Bat species	Guatemala	Hoar et al. (1998)
Eastern equine encephalitis virus	Bat species	Guatemala	Hoar et al. (1998)
Bat-variant rabies virus	Bat species	USA	McCull et al. (2000)
Australian bat Iyssavirus	Flying foxes <i>Pteropus</i> spp. yellow-bellied sheath-tail bat <i>Saccolaimus flaviventris</i>	Australia	Hanna et al. (2000)
Hendra virus	Flying foxes <i>Pteropus</i> spp.	Australia	Field et al. (2001)
Menangle virus	Flying foxes <i>Pteropus</i> spp.	Australia	Philbey et al. (1999)
Nipah virus	Flying foxes <i>Pteropus</i> spp.	Malaysia, Thailand, Cambodia, Bangladesh	Johara et al. (2001), Olson et al. (2002), Hsu et al. (2004), Wacharapluesadee et al. (2005)
Severe acute respiratory syndrome (SARS)-like coronavirus	Horseshoe bats (<i>Rhinolophus</i> spp.)	China	Lau et al. (2005) and Li et al. (2005)
Ebola virus	Old World fruit bats <i>Hypsignathus monstrosus</i> , <i>Epomops franqueti</i> , <i>Myonycteris torquata</i>	Gabon, Republic of Congo	Leroy et al. (2005)

peninsular Malaysia and Sumatra (Smith et al., 2005). In Malaysia, flying foxes forage up to 50 km from their roosting sites, often including commercial orchards populated by domestic animals (Epstein unpublished obs; Smith et al., 2005). Feeding on fruit trees on farms that contain a high density of domestic animals (e.g. pigs) increases the risk of pathogen transmission from flying foxes to domestic amplifier hosts (Chua et al., 2000). Hence, flying foxes may act as highly efficient vectors for the dispersal of viruses over considerable distances and thus allow contact of pathogens between animal populations that would not otherwise occur.

Most flying foxes are gregarious and roost in dense colonies resulting in frequent opportunities for direct and indirect contact between large numbers of individuals (Hall and Richards, 2000). Mating periods include particularly high rates of contacts between individuals (Markus and Blackshaw, 2002). Colonies may also consist of multiple flying fox species, which can increase roost size and density. This increases opportunities for transfer of pathogens between individuals and hence the number of secondary infections that may arise from a single infected individual in a population.

Maximum colony sizes of a number of flying fox species have decreased in recent times but some still occur in the hundreds of thousands (Richards, 2002). A large population size is often required to meet threshold conditions for pathogen establishment and to generate sufficient susceptible individuals, through births or immigration, to allow for pathogen persistence (Anderson and May, 1991). Epidemiological models, supported by empirical studies, show a strong link between host population size and density, and the spread and diversity of directly transmitted pathogens (Altizer et al., 2003).

For pathogens with short infectious periods and to which hosts develop long-lived immunity, such as henipaviruses, the disease may spread and individuals recover so quickly that very large populations are required for persistence (Lloyd and May, 1996). A metapopulation structure (in which infection persists via spatially discrete 'patches' where infection dies out sequentially rather than simultaneously) may enable

persistence, with lower overall population size, in such circumstances. However, for persistence to occur, there need to be enough patches of sufficient size to maintain infection across the metapopulation while ensuring its absence from each patch long enough for the number of susceptibles to replenish prior to the reintroduction of infection (Bolker and Grenfell, 1995).

A spatially heterogeneous population structure of flying foxes and periodic nomadic movements is consistent with this scenario. Population structure has been studied in very few flying fox species. Webb and Tidemann (1996), using allozyme electrophoresis and Random Amplified Polymorphic DNA (RAPD) analyses, concluded that three Australian flying fox species grey-headed flying fox (*Pteropus poliocephalus*), black flying fox (*Pteropus alecto*) and little red flying fox (*Pteropus scapulatus*) did not exhibit significant population structuring. However Vardon and Tidemann (1997) suggested that genetic differences did occur in *P. alecto* throughout its Australian range, due to size and colour variation of the species and geographical variation in the timing of reproduction. Preliminary results of a current study of mitochondrial DNA in this species also support the presence of population structuring (Breed et al., unpublished data).

An effective metapopulation may occur with occasional contact between several flying fox species that share a single virus species, as proposed for Hendra virus in Australia (Field et al., 2001). Although the majority of flying fox species have limited distributions (68% confined to land areas less than 50,000 km²), species known to host henipaviruses have the largest geographic distributions (Rainey and Pierson, 1992; Field et al., 2001). All of the five species of flying fox with distributions of over one million km² (*P. alecto*, *P. poliocephalus*, *P. scapulatus*, *P. vampyrus* and the Indian flying fox (*Pteropus giganteus*)) are thought to be important hosts of henipaviruses (Field et al., 2001; Hsu et al., 2004). The flying foxes with large-geographic distributions are also those that appear to show the greatest individual movements, often due to a migratory or nomadic lifestyle where the animals track patchily distrib-

uted food resources (Palmer et al., 2000). This results in these species having considerable potential to act as reservoirs for, and also vectors and disseminators of, viruses or other pathogens.

Flying fox populations occasionally exhibit episodes of mass mortality and or mass abortion that may be due to infectious diseases (Flannery, 1989; Hall and Richards, 2000; Messenger et al., 2003). Although detailed veterinary or epidemiological investigations have not been conducted into the cause of these events, there is apparent spatial and temporal association with clinical disease in some species: In the early 1930s populations of Marianas flying foxes (*Pteropus mariannus ualonus*) in the Caroline Islands of Kosrae, Micronesia, were reported to be reduced. Local residents reported that nearly all the bats had died in a recent epidemic that coincided with an outbreak of measles in the human population (Coults, 1931). Although henipaviruses and measles virus belong to the same family, it is unknown if either is able to infect *P. mariannus*. In the mid-1940s Degener (1949) reported that a disease epidemic had drastically reduced a population of the insular flying fox (*Pteropus tonganus*) near Savusavu in Fiji. More recently, Flannery (1989) reported two epidemics causing mass mortalities of flying foxes on Pacific islands. Firstly in 1985 on Manus, Admiralty Islands, numerous Bismarck flying foxes (*Pteropus neohibernicus hilli*) were found dead or dying over a period of a few weeks. Deaths over a short length of time such as this suggests an infectious agent is more likely to be responsible for the deaths than climatic factors, exposure to toxic substances or other environmental causes. Admiralty flying foxes (*Pteropus admiralitatum*) which also occur on Manus were apparently unaffected as were populations of *P. neohibernicus* on nearby islands. Flannery (1989) also reported a die-off of the Solomon Islands flying fox (*Pteropus rayneri grandis*) occurred in 1987 in Bougainville and Buka, northern Solomon Islands, and found evidence of a disease epidemic of flying foxes on Choiseul, Solomon Islands. The introduction of a pathogen by humans or domestic animals has been suggested as a possible cause of the apparent epidemics of Pacific island flying fox populations (Pierson and Rainey, 1992). However scientific evidence to support this theory is lacking. Finally, Hall and Richards (2000) report two mass abortion events occurring in flying fox colonies in Australia. In 1978 several thousand close-to-term fetuses were aborted in a colony of *P. poliocephalus* near Beenleigh, Queensland, and in 1983 a similar event occurred in another colony of *P. poliocephalus* at Indooroopilly Island, Queensland. A clear causal link between infectious disease and bat population declines or concurrent disease in other species has yet to be established. Structured epidemiological and pathological investigations of future outbreaks are needed to address this situation.

The Action Plan for Australian Bats (Duncan et al., 1999) states that the perceived risk to humans from bat diseases has reduced public enthusiasm for the conservation of flying foxes. One Australian study found the public perception of bats to be that they are unclean and a threat to the health of adults and children (Scott, 2000). The perceived risk of human disease from a wildlife reservoir has led to persecution of other species, e.g. birds following recent outbreaks of avian influenza, badgers as a risk of tuberculosis in the UK, bison as a risk of brucellosis in the Greater Yellowstone Area (Daszak and Cunningham, 2002).

5. Hendra and Nipah virus emergence

Hendra virus, initially called equine morbillivirus, was first described in 1994 in Australia and was associated with an outbreak of acute respiratory disease in horses. Twenty-one horses and two humans (the trainer and a stablehand) became infected, with the resultant deaths of 14 of the horses and the trainer (Baldock et al., 1996; Murray et al., 1995). In a further four foci (in 1994 (Hooper et al., 1996; Rogers et al., 1996), 1999 and 2004 (Field, 2005)) another five horses and two humans were infected, all five horses and one person fatally so. The four human cases have all been attributed to exposure to infected horses (Field, 2005; O'Sullivan et al., 1997; Selvey et al., 1995). Initial hypotheses as to the origin of Hendra virus included contaminated biological products, illegal performance-enhancing substances and malicious intent (Douglas, 1998). When initial investigations failed to support any of these scenarios, consideration was given to the possibility of a wildlife reservoir. Initial surveillance of wildlife, which focused primarily on terrestrial species, found no evidence of Hendra virus infection. Subsequent wildlife surveillance adopted a targeted approach, with species prioritised on: (1) their presence at the outbreak locations, (2) their ability to move between locations, or the existence of overlapping, mixing populations spanning the locations, and (3) plausible contact between the wildlife species and horses (Young et al., 1996, 1997). Several avian species and two species of flying fox, met the criteria. Flying foxes were given a higher priority for further investigation based on the apparent mammalian predilection of the virus (Westbury et al., 1995) and on reports of paramyxovirus infections in bats elsewhere (Henderson et al., 1995; Pavri et al., 1971). Serological evidence of Hendra virus infection was promptly identified in *P. alecto*. Further investigations suggested Hendra virus infection was endemic in all four species of flying fox on mainland Australia (*P. alecto*, *P. poliocephalus*, *P. scapulatus* and *Pteropus conspicillatus*), and flying foxes were identified as a natural host and probable reservoir of this virus (Field, 2005).

Nipah virus was first described in 1999 following an outbreak of disease in pigs and humans in peninsular Malaysia (CDC, 1999a,b). Over one million pigs were culled to contain the outbreak. Of 265 reported human cases, 105 were fatal. Direct contact with infected pigs was identified as the predominant mode of human infection (Chua et al., 2000; Goh et al., 2000). Molecular evidence indicated that Nipah virus and Hendra virus were closely related (CDC, 1999a). Since flying foxes were the likely reservoir of Hendra virus in Australia, Malaysian bat species were prioritised for surveillance. In common with most countries in the south-east Asian region, Malaysia has a great diversity of bat species. There are at least 13 described species of Old World fruit bat (family Pteropodidae), including two flying fox species, and 100 described species of insectivorous bats (suborder Microchiroptera) in peninsular Malaysia alone (Hutson et al., 2001; Liat, 2001). Blood and tissue samples were collected from 324 bats from 14 species and *P. vampyrus* and *P. hypomelanus* were identified as likely natural and reservoir hosts due to the high percentage of individuals showing antibodies to Nipah virus (i.e. evidence of prior exposure to the virus) (Johara et al., 2001). Subsequent isolation of virus from *P. hypomelanus* supported this contention (Chua et al., 2002).

Five outbreaks of Nipah virus-associated disease in humans have been described in Bangladesh between April 2001 and February 2005 (Anon, 2004a,b, 2005; Hsu et al., 2004). As of 11 February 2005, a total of 122 cases had been recognised by the Bangladesh Directorate of Health Services, at least 78 (64%) of which were fatal (Field et al., in press-b). A number of the characteristics of the Bangladesh outbreaks are similar to the outbreak in Malaysia; delayed recognition, a primary presentation with fever and central nervous system signs, and a high case fatality rate. However, in marked contrast to the Malaysian outbreak, infection in humans was not associated with disease in pigs, and there is evidence of horizontal human transmission. Further, the pattern of the Bangladesh outbreaks suggests a sporadic, geographically scattered introduction of infection to humans. Nucleotide sequence data also supports a different epidemiology in Bangladesh. Overall, the nucleotide sequences of the genomes of the Nipah viruses isolated in Bangladesh in 2004 and Malaysia in 1999 share 92% identity. While the size and distribution of the open reading frames and the sequences of key regulatory elements are conserved, the amount of genetic diversity in sequences obtained from Malaysia and Bangladesh varies (Harcourt et al., 2005). Those obtained from human cases in Malaysia suggest a single source of human infection from the porcine amplifying host (AbuBakar et al., 2004; Chan et al., 2001; Chua et al., 2000); whereas those from Bangladesh form a cluster that is clearly distinct from the Malaysian sequences, but differ from each other by approximately 0.8%, suggesting multiple introductions of the virus to humans.

6. Processes driving henipavirus emergence

Hendra and Nipah appear to be ancient viruses that co-evolved with, and are well adapted to, their natural flying fox hosts (Gould, 1996; Murray et al., 1995). The emergence of these viruses in humans has required a bridge from the natural host to a susceptible ‘spillover’ host. Such bridges typically result from changes to the agent, the host, or the environment. The close RNA sequence match between flying fox, livestock and human isolates of Hendra and Nipah viruses suggests that emergence is more likely associated with ecological changes that have promoted contact between bats and livestock, rather than with genetic change leading to increased virulence (Li et al., 2005).

Flying foxes generally display roost-site fidelity, staying in the same location for as long as adequate food resources are available and the site remains undisturbed (Hall and Richards, 2000). Hence some flying fox roost sites are occupied throughout the year while other sites are seasonally occupied (Gumal, 2004; Nelson, 1965). In Australia, *P. poliocephalus* have been shown to forage up to 50 km from roost sites and more than 2000 km over four months (Eby, 1991; Tidemann and Nelson, 2004). In Malaysia, *P. vampyrus* forages within a 30-km radius of its roosting site but has been shown to move hundreds of kilometres within a 10-day period (Epstein et al, unpublished data; Hodgkison et al., 2004). Available data on many flying fox species suggest that populations in Australia and south-east Asia are declining with disruption occurring throughout their range. In south-east Asia, anthropogenic activities (primarily habitat destruction and hunting) constitute major

threats. Deforestation, whether for agricultural land, commercial logging, or urban development, is widespread and results in loss or abandonment of roosting sites, and the loss of feeding habitats. This habitat loss due to clearing is often exacerbated by tropical storms as the remnant forest may be particularly prone to high wind damage. Hunting, whether for consumption, sport or crop protection, at both a local and commercial level, results in the abandonment of roost and feeding sites (Mickleburgh et al., 1992). A scenario thus emerges of flying fox populations under stress, with altered foraging and behavioural patterns, of niche expansion, and of closer proximity to man. In Australia, the geographical redistribution of roosting sites has been increasingly into urban areas in recent decades (Hall and Richards, 2000).

Four hypotheses have been proposed as possible drivers of emergence of Nipah virus in peninsular Malaysia.

1. That El Niño Southern Oscillation (ENSO)-related haze from wide-scale forest fires in Sumatra and Kalimantan in 1997 may have led to the emergence of Nipah virus in Malaysia by causing a massive influx of flying foxes into northern Peninsular Malaysia from Indonesia (Chua, 2003). This hypothesis relied upon two key assumptions: that rare and unfavourable conditions (e.g. intense haze and forest fires) were required to cause bats to fly between Sumatra and Malaysia; and that bats had not previously inhabited the region where Nipah virus emerged; or if they had, then these bats did not carry Nipah virus (Daszak et al., 2006). Recent epidemiological studies have shown that Nipah virus is widely distributed in both *P. vampyrus* and *P. hypomelanus* throughout Peninsular Malaysia (Abdul Rahman, unpublished data). Also, satellite telemetry studies have shown bats flying between Sumatra and Malaysia in a non-ENSO year and in the absence of an extreme haze event (Smith et al., 2005). Though it is still unclear how human activities such as land-use change alter long-range movements of flying foxes in Malaysia, it is apparent that these animals move throughout peninsular Malaysia, and between Sumatra, Thailand, and Malaysia (Daszak et al., 2006).
2. That unsustainable hunting of flying foxes has resulted in localised niche vacuums (‘sinks’) with relative resource abundance, creating regional gradients along which neighbouring bat populations move, resulting in a net movement of virus into human-inhabited areas and hence an increase in probability of effective contact and spillover.
3. That regional deforestation has changed the seasonal foraging movements of flying foxes and led to an increased reliance on horticultural crops, resulting in a relative increase in the density of bats proximate to human and livestock populations.
4. That the marked increase in the number, density and distribution of the Malaysian pig population in the last 10 years has led to an increased probability of contact between flying foxes and pigs. This has been further enhanced by the planting of fruit orchards immediately adjacent to piggeries (Daszak, 2005).

These hypotheses are not mutually exclusive. The key events leading to emergence of Nipah virus in Malaysia appear to include changes to the pig industry and the continual

presence of Nipah virus within flying fox populations that habitually visit orchards next to piggeries.

7. Reservoir host management strategies

This section revisits a previous discussion of management strategies for henipaviruses (Field and Mackenzie, 2004), presenting management strategies for the natural, intermediate (spillover) and human hosts. Effective disease management requires an understanding of the epidemiology of the disease (knowledge of its cause, maintenance and transmission, host range of the aetiological agent, and the nature of the host–agent relationship), an ability to detect disease (surveillance and diagnostic capabilities) and political/public/industry support. Current strategies for the management of henipaviruses are generally directed at minimising direct or indirect contact with the natural host, monitoring intermediate hosts, improving biosecurity on farms, and better disease recognition and diagnosis (Field and Mackenzie, 2004).

The sporadic, and apparently rare, nature of Hendra virus spillover events from flying foxes to horses, the low infectivity for horses (and the consequent limited economic impact), and the apparent absence of direct transmission from flying foxes to people has resulted in more emphasis on management strategies for horses than of flying foxes. Quarantine of infected premises, movement controls on stock, and disinfection have so far proved effective strategies (Baldock et al., 1996). Hendra virus exclusion is routinely undertaken for horses exhibiting an acute respiratory syndrome in Queensland. Veterinarians involved in these disease investigations are advised to wear appropriate protective equipment and use a limited necropsy approach, as horses have been the source of infection for all four human cases. Putative risk factors for infection in horses appear to be age (>8 yo), breed (thoroughbred), housing (paddocked), season (late gestation or the birthing season of local flying fox populations), and the presence of favoured flying foxes food trees in the index case paddock (Field et al., in press-a). A considerable research focus on the ecology of Hendra virus is yet to define the route of virus excretion or any temporal pattern of infection in flying foxes. This information, and knowledge of the actual mode of flying fox-to-horse transmission would facilitate a risk management approach to spillover infection in horses.

In marked contrast to Hendra virus, the Nipah virus outbreak in peninsular Malaysia in 1999 had an enormous economic and social impact (Nor et al., 2000). Nipah virus was highly infectious for pigs, with all classes of pigs susceptible. The pattern of on-farm infection was consistent with respiratory transmission; between-farm spread was generally associated with the movement of pigs. An extensive post-outbreak surveillance program in Malaysia showed that farms that did not receive pigs at the time of the outbreak generally remained uninfected, even when neighbouring farms were infected. Human infections were predominantly attributed to contact with live pigs; none was attributed to contact with bats (Chua et al., 2000). Horizontal transmission was not a feature of infection in humans. Recommended host management strategies primarily target pig-to-pig transmission,

secondarily the flying fox–pig interface (that is, the natural host–spillover host interface). The central strategy has been the implementation of sound farm management practices, such as monitoring herd health and early recognition of disease syndromes. Furthermore, advanced planning for emergency management of disease outbreaks has been put in place. This involves established surveillance, detection, and emergency response capabilities.

While strategies directed at the flying fox–pig interface are limited by our incomplete knowledge of the ecology of Nipah virus, several simple on-farm measures can be taken to reduce the likelihood of spillover events occurring. The removal of fruit tree plantations from the immediate vicinity of pig sheds greatly reduces the probability of flying fox–pig contact. Similarly, the wire screening of open-sided pig sheds is a simple and inexpensive strategy to prevent direct contact between flying foxes and pigs. Indirect contact (with flying fox urine or faeces or partially eaten fruit) can be avoided by ensuring roof run-off does not enter pig pens (Chua, 2003).

Henipavirus spillover to domestic animals might be effectively controlled by the methods mentioned above but events in Bangladesh warn against complacency in elimination of the zoonotic risk of henipaviruses using these methods alone.

Management of a bat-borne zoonotic disease has been previously attempted for rabies virus. Historically, population reduction was used as a control strategy for vampire bats in Latin America. The methods used at that time are now generally considered inhumane, unethical and ineffective and some of the targeted species have become endangered in their natural environment (Arellano-Sota, 1988; Hanlon et al., 1998). Trap, vaccination and release programs using parenteral vaccination have been employed for rabies control of a few terrestrial wildlife species. However these methods are considered prohibitively expensive for large populations and logistically impossible for non-terrestrial species (Hanlon et al., 1998).

A study by Setien et al. (1998) showed that an oral vaccine was capable of inducing a protective immune response to rabies in vampire bats following oral vaccine delivery and hence an oral vaccination approach may be plausible for other bat species.

Mackenzie et al. (2003) discuss the possibility of use of an oral vaccine for henipaviruses in flying foxes in the future. They observe that the presence of antibodies to Hendra virus and Nipah virus in healthy flying foxes could warrant the inclusion of a biomarker in a vaccine to distinguish between vaccinated individuals and naturally infected individuals. Flying foxes are particularly partial to banana flavour which may be an appropriate attractant for use in vaccine baits. However, Mackenzie et al. (2003) caution that various aspects of flying fox behaviour require further study before development of an oral vaccine strategy.

Development of a vaccine for Hendra or Nipah virus suitable for use in wild flying foxes is not likely to occur in the near future. However, a better understanding of flying fox behaviour and ecology, henipavirus dynamics in flying foxes, and anthropogenic factors that facilitate spillover events will offer cost-effective and practical solutions for preventing future outbreaks.

8. Future perspectives

The emergence of the *Henipavirus* genus as a significant threat to public health in Southeast Asia and Australia during the last decade has highlighted the frequent perception of conflict between public health and conservation. With an increasing number of often lethal viruses identified as emerging from wildlife populations, proposals to cull or extirpate these reservoirs as a public health measure are increasingly likely. Fortunately, this does not seem to have occurred for *Pteropus* spp. bats, but after the global outbreak of SARS in 2002–2003 and the identification of civets as the likely source of human infection, just such measures were proposed by the Chinese authorities. The recent identification of *Rhinolophus* spp. bats as reservoirs for SARS-like coronaviruses brings this issue into direct focus (Lau et al., 2005; Li et al., 2005). We support a broad ecosystem health approach that endeavours to unravel the complex relationships between environment, reservoir host, humans and livestock, incorporating the fields of infectious disease ecology, eco-health, conservation medicine and others. These approaches all have a collaborative, trans-disciplinary thrust that investigates human population behaviour alongside disease dynamics and wildlife population dynamics (Daszak et al., 2004). Already, these studies have begun to demonstrate a new approach to public health protection that involves cur-tailing the anthropogenic environmental changes, or demographic/human behavioural risk factors ultimately responsible for disease emergence. This has clear benefits to both public health and conservation, and appears to be a promising avenue of future research.

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