

# The natural history of Hendra and Nipah viruses

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**ABSTRACT** – Pteropid bats (flying foxes), species of which are the probable natural host of both Hendra and Nipah viruses, occur in overlapping populations from India to Australia. Ecological changes associated with land use and with animal husbandry practices appear most likely to be associated with the emergence of these two agents. © 2001 Éditions scientifiques et médicales Elsevier SAS

Hendra virus / Nipah virus / flying foxes / virus transmission / epidemiology

## 1. Introduction

The emergence of a cluster of viruses in the Australasian region in the 5 years since 1994 has posed a number of questions relating to the natural history of these agents. Why did the viruses emerge at this time? What is their natural host(s)? What factors precipitated emergence? What are the spillover mechanisms? Do the natural hosts constitute a reservoir for further disease emergence? This article seeks to address these questions.

## 2. The emergence of Hendra virus in Australia

In September 1994, a sudden outbreak of an acute respiratory syndrome in thoroughbred horses in a training complex in Brisbane in the state of Queensland resulted in an immediate shutdown of the horse racing industry in southeast Queensland. The syndrome was characterised by severe respiratory signs and high mortality. Thirteen horses died acutely. The causal agent was unknown. Exotic diseases including African horse sickness were excluded, as were a number of toxic agents. Quarantine procedures and movement restrictions were immediately put in place, and epidemiological investigations were commenced. The outbreak was contained, and within days, a virus, the putative causal agent, had been identified. The virus, a previously undescribed member of the family Paramyxo-

viridae, was initially named equine morbillivirus, but was subsequently re-named Hendra virus (HeV), after the Brisbane suburb where the outbreak occurred [1, 2].

The putative index case was a heavily pregnant thoroughbred mare at pasture in suburban Brisbane. When observed to be ill, she was moved to a training stable housing 23 thoroughbreds to facilitate nursing. The mare died after a 2-day illness. A further 12 horses in the stable and an adjoining training stable died within the next 14 days. There were four non-fatal cases, two of which were left with mild neurological signs. Clinical signs included fever, facial swelling, severe respiratory distress, ataxia, and terminally, copious frothy nasal discharge (blood-tinged in some horses). A further three horses in the stable were subsequently found to have seroconverted in the absence of obvious clinical signs. All seven were subsequently euthanased [2, 3]. The new virus demonstrated its zoonotic capability when the trainer and a stablehand became ill. Both were closely involved with the nursing of the index case, and both became ill with a severe influenza-like illness within 1 week of the death of the index case, and prior to clinical signs in other horses. The trainer was hospitalised and subsequently died after respiratory and renal failure. Infection with HeV was demonstrated in both human cases [4].

In October 1995, a second HeV outbreak in horses was retrospectively diagnosed after the HeV-attributed death of a thoroughbred stud-owner who suffered a relapsing encephalitic disease. This second focus (near Mackay in central Queensland, almost 1 000 km north of Brisbane) chronologically preceded the Brisbane outbreak by several weeks, and resulted in the death of two horses. The first horse, a 10-year-old heavily pregnant thoroughbred

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mare died on August 1, 1994 after exhibiting severe respiratory distress, ataxia, and marked swelling of the cheeks and supraorbital fossa over a 24-h period. The second horse, a 2-year-old colt in an adjoining paddock was reported to have direct contact (through the fence) with the dead mare. The colt died 11 days later, again after a 24-h clinical course, during which he exhibited aimless pacing, muscle trembling and haemorrhagic nasal discharge. Histopathological examinations at the time were inconclusive in both cases. Avocado poisoning and brown snake bite were considered as differential diagnoses [5–7].

Extensive investigations (including targeted serological surveys of livestock, and traces of livestock movements) were undertaken in relation to each of these outbreaks. No anti-HeV antibodies were detected in over 5 000 domestic animals (including 4 000 horses, plus cattle, dogs, cats and poultry) [5, 8, 9], and no epidemiological link between the two outbreak sites could be identified (Douglas I.C., unpublished results). The pattern of the Brisbane outbreak suggested that HeV infection was not highly contagious in horses, and that direct contact or mechanical transmission of infectious body fluids was necessary for natural transmission to occur [3]. Retrospective investigation of diagnostic laboratory records and stored specimens failed to identify any instances of previous infection in horses (Ketterer P.J., unpublished results; Hooper P.T., unpublished results).

In January 1999, four and a half years after the previous cases, a new fatal case of HeV infection was reported in a horse near Cairns in north Queensland. The affected horse was again an aged thoroughbred mare at pasture. Clinical signs included inappetence, depression and swelling of the face, lips and neck. Despite symptomatic treatment, the mare deteriorated and was found recumbent the next morning with copious quantities of yellow frothy nasal discharge. She was euthanised. A companion horse was unaffected on clinical or serological examination [10, 11].

### 3. The emergence of Nipah virus in Malaysia

A major outbreak of disease in pigs and humans in Peninsular Malaysia between September 1998 and April 1999 resulted in the death of 105 humans [12] and the eventual culling of about 1.1 million pigs (Ong B.L., unpublished results). The disease in pigs was highly contagious, and characterised by acute fever with respiratory involvement and sometimes nervous signs in all age classes. Sows and boars sometimes died peracutely [12, 13]. The predominant clinical syndrome in humans was encephalitic rather than respiratory, with clinical signs including fever, headache, myalgia, drowsiness, and disorientation sometimes proceeding to coma within 48 h [14, 15]. The majority of human cases had a history of direct contact with live pigs. Most were pig farmers.

Initially attributed to Japanese encephalitis virus, the primary disease aetiology in pigs and humans was subsequently shown to be a previously undescribed virus of the family Paramyxoviridae. Preliminary characterisation of the isolate at the Centers for Disease Control and Preven-

tion (CDC) in Fort Collins and Atlanta, USA, showed the new virus, subsequently named Nipah virus (NiV), had ultrastructural, antigenic, serologic and molecular similarities to HeV [16], the recently emerged and zoonotic virus described in Australia in 1994. Epidemiological evidence suggested that the primary means of spread between farms and between regions was the movement of pigs. The primary mode of transmission on pig farms was believed to be via the respiratory route, and was subsequently confirmed so by laboratory evidence (Middleton D., unpublished results). Retrospective investigations suggest that NiV has been responsible for disease in pigs in Peninsular Malaysia since late 1996, but was not recognised as a new syndrome because the clinical signs were not markedly different from those of several endemic diseases, and because morbidity and mortality were not remarkable [17].

### 4. Investigations of the origins of HeV

To evaluate the theory that HeV existed in a wildlife reservoir, a preliminary serological survey of wildlife species was undertaken in May and November 1995, focused on the immediate locations of the equine index cases. Later, the sample base was broadened to include sick or injured wildlife in temporary captivity with wildlife carers and veterinary practitioners. No evidence of HeV infection was found in 168 individuals from more than 16 species of rodents, marsupials, birds, amphibians and insects tested. However the small sample size for any particular species limited meaningful interpretation of the negative findings, and indicated the need for a more targeted approach to wildlife surveillance.

In a subsequent prioritisation of possible host species for surveillance, the following criteria were applied: the target species should be present in both outbreak locations; the species should be capable of moving between the two locations, or have overlapping, mixing populations spanning the two locations, and contact between the target species and horses should be plausible [18]. Several species of nomadic birds and pteropid bats (flying foxes) met the criteria. Flying foxes were given a higher priority for further investigation based on the apparent mammalian predilection of the virus, and reports of paramyxovirus infections in bats elsewhere, namely a rubulavirus (Mapuera virus) in a bat in Brazil [19], and a parainfluenza virus in a flying fox in India [20].

Opportunistic sampling of sick or injured wild flying foxes in temporary captivity was employed as a means of screening wild flying fox populations. While primarily a methodology of convenience, it was recognised that the potentially positive bias of the opportunistic sample could maximise the likelihood of detecting evidence of infection (assuming infection with HeV predisposed flying foxes to becoming 'sick or injured'). In April 1996, anti-HeV antibodies were identified in a black flying fox (*Pteropus alecto*) in central Queensland, and within weeks, in grey-headed flying foxes (*Pteropus poliocephalus*), little red flying foxes (*Pteropus scapulatus*), and spectacled flying foxes (*Pteropus conspicillatus*) at several locations in

Queensland [18]. In September 1996, 2 years after the first reported outbreak of HeV infection in horses in Brisbane, a Hendra-like virus was isolated from the reproductive tract of an apparently healthy, pregnant grey-headed flying fox (*P. poliocephalus*) euthanised after becoming entangled on a wire fence. Comparison of the bat isolate (tentatively called bat paramyxovirus at the time) with the isolate from horses showed it to be indistinguishable from HeV by a range of tests [21]. A serologic survey of 1 043 non-randomly sampled flying foxes of the above four mainland Australian species collected from multiple Queensland locations between 1996 and 1998 revealed a crude HeV seroprevalence of 47%. Similar frequencies were subsequently identified in additional samples taken at locations across the Australian mainland range of flying foxes during the same period. In addition, in a retrospective serological survey of Australian flying foxes, anti-HeV antibodies have been identified in sera collected in 1982, the earliest sample tested (Field H.E., et al., unpublished results).

The described occurrence and frequency of anti-HeV antibodies in flying foxes is consistent with an endemic pattern of infection Australia-wide. This interpretation is supported by the absence of gross pathology or attributable illness in naturally infected (Field H., Halpin K., unpublished results) or experimentally infected [22, 23] flying foxes, indicating that infection in flying foxes may be largely sub-clinical. These features identify flying foxes as the probable natural host of HeV.

Transmission from flying foxes to horses has not been demonstrated; however, experimental infections in a range of species, and investigations of natural infections in flying foxes and in horses have suggested possible modes of transmission. Virus has been isolated from the kidney, urine and (less so) oral cavity of horses, and the kidney and urine of cats experimentally infected with HeV. Horses have been infected experimentally by the naso-oral route, and cat-to-cat transmission and suspected cat-to-horse transmission have been reported [22, 24]. These transmissions are believed to most probably have resulted from exposure to infected urine. Respiratory spread has not been demonstrated experimentally. Observations of the pattern of spread of infection within the stables in the Brisbane outbreak suggested that mechanical transfer occurred, with the possibility of terminal frothy nasal discharge being the source of virus. Spread by urine was considered unlikely within the stable environment (Douglas I.C., unpublished results). The possibility of contact with nasal discharge as a means of horse-to-horse transmission is consistent with a report of the second case in the Mackay episode having licked the face of the recently dead index case (Douglas I.C., unpublished results). It has been hypothesised that spillover from flying foxes to horses is effected by contact with infected foetal tissues or fluids, most probably via the ingestion of recently contaminated pasture [10, 21, 25]. This hypothesis was initially based largely on the temporal overlay of disease events in horses with the birthing period of species of flying fox in Queensland, and on the absence of evidence of infection in wildlife rescuers regularly exposed to flying fox excreta. It

is supported by the isolation of virus from foetal tissues of naturally infected [21] and experimentally infected flying foxes [23].

Notwithstanding, and albeit that HeV has not been isolated from the urine of flying foxes to date, exposure to infected urine cannot be excluded as a spillover mechanism, given the previously described isolations from the urine of experimentally infected horses and cats. A novel possible spillover mechanism currently being revisited (Field H.E., Markus N., Booth R., unpublished results) is the ingestion by horses of the masticated pellets of residual fruit pulp spat out by flying foxes feeding on fibrous fruit. The quantity of these 'spats' under fruiting trees can be substantial, and could present a plausible, attractive and viable source of virus to grazing horses. The possibility of vector-mediated transmission, particularly in relation to flying fox to flying fox transmission has also received some attention. Pooled samples of *Cyclopodia albertisii* (family Nycteribiidae), obligate blood-sucking ectoparasites of pteropid flying foxes have been screened using PCR methodology with negative results (Field H.E., unpublished results). Blood-fed mosquitoes were included in the initial wildlife investigations on the Brisbane and Mackay index properties [5]. While one pooled sample produced a positive HeV PCR product (Gould A.R., unpublished results), subsequent screening of mosquitoes at multiple locations and times has failed to identify any other positive samples (Field H.E., unpublished results). The transmissibility of HeV in laboratory infections has been low [22, 24, 26], supporting field observations of naturally infected horses [3]. In contrast, the high seroprevalence in surveyed flying fox populations is consistent with high transmissibility in these species in the wild (Field H.E., unpublished results).

## 5. Investigations of the origins of NiV

Surveillance of wildlife species for evidence of the origin of NiV was an integral part of the outbreak investigation, and as the outbreak in pigs and humans came under control, the focus of part of the investigating team shifted to identifying the source of the infection in pigs. A number of factors influenced the wildlife surveillance methodology employed: the limited time and resources; the demonstrated similarities between NiV and HeV [16]; targeted wildlife surveillance had proved an efficient and successful alternative to the initial 'wide-net' approach in the HeV wildlife investigations in Australia [18].

Knowledge of the similarities between NiV and HeV was of key importance in planning an effective wildlife surveillance strategy for NiV. This scenario was in marked contrast to the state of knowledge of HeV at the time of the initial investigations into the natural host of that virus, when the absence of known closely related viruses (which might suggest a preliminary line of investigation) necessitated initial wildlife investigations being carried out on a broad taxonomic front. Thus when laboratory evidence indicated that NiV and HeV were closely related, Malaysian bat species became a logical surveillance priority. In common with most countries in the southeast Asian region,

Malaysia has a great diversity of bat species. There are at least 13 species of fruit bat (sub-order Megachiroptera), including two flying fox species, and at least 60 species of insectivorous bats (sub-order Microchiroptera) described in peninsular Malaysia alone [27]. In the Australian HeV investigations, an opportunistic sampling methodology was adopted as a means of screening wild flying fox populations, but because wildlife rescue networks are less extensive in Malaysia, this approach was not a realistic option in the NiV investigations, and wild-caught bats were targeted. Over a 5-week period, bat populations at ten locations across four states on peninsular Malaysia were non-randomly sampled by mist-netting or shooting with the assistance of the Malaysian Department of Wildlife and National Parks. Sampling locations included, but were not restricted to, NiV disease outbreak areas. Blood and tissue samples were collected from 324 bats from 14 species and submitted for serology and virus isolation (Field H.E., Johara M.Y., unpublished results). Neutralising antibodies to NiV were found in 21 bats from five species (four species of fruit bat, including two flying fox species, and one insectivorous species). Cross-neutralisation of Nipah antigen by antibodies to HeV was excluded as the cause of the reactivity; however, a low level of cross-reactivity with HeV antigen (with at least a four-fold lower titre) was detected in 1/21 bats with neutralising antibodies to NiV. All culture harvests were negative for NiV antigen, and all attempts to amplify NiV RNA were also negative (Field H.E., Johara M.Y., unpublished results). A more recent attempt to isolate NiV from a seropositive colony of flying foxes appears to have met with success. While sequencing is incomplete at the time of writing, an isolate from pooled urine samples has produced characteristic cytopathic effect in Vero cells, has reacted strongly with Nipah antibody and less so with Hendra antibody, and has yielded PCR products of the same size as those from human Nipah isolates (Chua K.B., Lam S.K., unpublished results).

Although fruit bats were suspected as the primary natural reservoir for NiV, the efficient maintenance and transfer of virus in pig populations was an indication that the potential secondary host range might be large. Peridomestic small mammals such as rats and house shrews were common in and around the pig farms. In addition, dogs were observed to share living space with pigs, and sick dogs with evidence of infection with NiV were discovered early in the investigation. A screening of peridomestic animal populations, including rats, dogs, chickens, jungle fowl, and other domestic animals, was undertaken using opportunistic and structured methodologies (Mills J., Asiah, Bunning M., Ksiazek T., unpublished results). Whole blood was collected to test for IgG antibody to HeV by enzyme immunoassay, and organ tissues were frozen in liquid nitrogen and conserved in formalin (except from animals not sacrificed, such as pet dogs, and healthy livestock). Sample collection followed established methods and safety guidelines [28].

The most frequently captured small mammal was *Rattus rattus*, followed by other species of *Rattus* and the insectivore *Suncus murinus* (the house shrew). Birds sampled and tested were primarily chickens, jungle fowl

(*Gallus gallus*), domestic ducks, and pigeons (*Columba livia*). No antibody was detected in 110 birds, 316 rodents, or 37 insectivores tested. Of 465 dog samples tested, 72 had antibody, an overall prevalence of 15%. Opportunistic sampling in March and April demonstrated a 46% antibody prevalence in about 92 dogs that were sampled from the disease-endemic areas in the vicinity of Bukit Pelandok. In the intensive transect study during May, only four antibody positive dogs were found among 249 tested; all of these dogs were sampled from within approximately 5 km of the disease endemic area. An additional 114 dogs sampled from veterinary clinic and pounds in the Kuala Lumpur area were all negative.

The uniformly negative serologic results from peridomestic rodents, insectivores, and birds indicate that these animals did not play a role as secondary reservoirs for NiV after pigs were removed from the community. The initially high prevalence of infection in dogs in the endemic area during and immediately following the removal of pigs indicates that dogs readily acquired infection following close association with infected pigs. Nevertheless, the much lower antibody prevalence and restriction of infection to within 5 km of the endemic area indicated that NiV did not spread horizontally within dog populations.

## 6. Flying fox distribution and ecology

There are about 60 species of bats in the genus *Pteropus* and which are commonly referred to as flying foxes. The world distribution of flying foxes extends from the western Indian Ocean islands of Mauritius, Madagascar and Comoro, along the sub-Himalayan region of Pakistan and India, through southeast Asia, Philippines, Indonesia, New Guinea, southwest Pacific Islands as far east as the Cook Islands, and Australia excluding Tasmania. They are not found on mainland Africa, Europe, Asia or North and South America. Thus they are often called Old World fruit bats, and based on their greatest diversity, originate from Sulawesi and eastern New Guinea, where up to six species are found. Many species are restricted to islands, but a number are widespread. Flying foxes range in body weight from 300 g to over 1 kg, and in wingspan from 600 mm to 1.7 m. They are the largest bats in the world, do not echolocate and navigate at night by eyesight and their keen sense of smell. Females usually have only one young a year after a 6-month pregnancy. The young grow rapidly but are dependent on their mother for up to 3 months. All species eat plant products (most commonly fruits, flowers and pollen) and roost communally in trees [29–32].

There are seven species of flying foxes recorded for Australia. One is probably extinct (*Pteropus brunneus*), and two are restricted to the islands of Torres Strait (*Pteropus banakrisi* and *Pteropus macrotus*). Four species are found on the Australian mainland. Only the grey-headed flying fox (*P. poliocephalus*) is endemic to Australia, and is found from Melbourne along coastal eastern Australia to Bundaberg in southern Queensland. In Australia, black flying foxes (*P. alecto*) are found from Kempsey north around the coastal areas of Queensland, Northern Terri-

tory and northern Western Australia down to about Carnarvon. Spectacled flying foxes (*P. conspicillatus*) are restricted to the wet tropics of Queensland and little red flying foxes (*P. scapulatus*) have been recorded over a large part of the eastern, northern and western parts of the Australian continent. All three are known to occur in New Guinea. The regional distribution of the black flying fox extends across to the Indonesian islands of Sulawesi, Lombok, Kangean and Baeween. The spectacled flying fox is found over coastal New Guinea and on the Indonesian island of Halmahera [29, 30].

Flying foxes are known to travel over considerable distances. Radio-tagged grey-headed flying foxes in eastern Australia have been shown to undertake regular long distance movements covering up to 600 km (Grafton to Nowra). The species is also known to move from one camp to another following good flowering of native trees. These movements cause fluctuating numbers in their camps and indicate that over their whole range the population is in a state of flux [33, 34]. There is strong anecdotal evidence that little red flying foxes may move over even greater distances and areas, but on an irregular basis. There are no data on movements of black or spectacled flying foxes. Observations on flying fox movements in Torres Strait showed a yearly movement cycle which involved flying foxes moving into the islands from New Guinea, down to Cape York and back into New Guinea. Two species, the black and large-eared were the principal flying foxes involved in these movements [35]. The large-eared flying fox is also found on islands along the southern coast of New Guinea and several nearby Indonesian islands.

Generally, where more than one species of flying fox are found, camps are shared by several species. In northern Australia, black and spectacled flying foxes share camps with each other, and in New Guinea and Indonesia, with other species of flying foxes [29, 36]. The possibility of movements of flying foxes between New Guinea and Indonesian islands and onto Southeast Asia has never been studied. There is however, anecdotal evidence that flying foxes can cross large distances over water, albeit inadvertently. There is record of a little red flying fox in New Zealand, 2 000 km from its southernmost Australian occurrence, and a sighting of Indian flying foxes (*Pteropus giganteus*) 320 km from land [32, 37]. Both reports are believed to be of animals that have been blown off shore by strong winds.

It is noteworthy that the overlapping distributions of only three species of flying foxes are needed to form a continuous link between the east coast of Australia and Pakistan. Black and spectacled flying foxes are known to mix with the island flying fox (*Pteropus hypomelanus*) and the Malayan flying fox (*Pteropus vampyrus*) in New Guinea and Indonesia and these species, at the northern extent of their range, are known to mix with the Indian flying fox (*P. giganteus*), whose distribution extends eastward (from Thailand and Burma) to India and Pakistan [30, 38]. This link can be demonstrated with two separate groups of flying foxes.

## 7. Factors contributing to infectious disease emergence

During the middle part of the 20th century, the use of antibiotics and vaccines, and improvements in sanitation and water quality dramatically decreased the incidence of infectious diseases to the extent that in 1967, the then Surgeon General of the United States, declared that it was time to “close the book on infectious diseases”. That optimistic view was short-lived. In 1998, Surgeon General David Satcher identified infectious disease as the number one killer worldwide, and spoke of the “continuing threat of emerging infectious diseases”. In the United States, according to Dr Satcher, the death rate from infectious diseases, excluding AIDS, rose by 22% between 1980 and 1992. The stark difference in perspective between these two surgeons general is a result of our recent increased awareness of what is now referred to as ‘emerging infectious disease’. Although emerging infectious disease is best documented in the context of human disease, the term is equally applicable to diseases of wildlife [39], and recent research into diseases such as those caused by Nipah and Hendra viruses illustrates that emerging diseases of humans and wildlife may be closely intertwined.

The term ‘emerging’ can be used to describe diseases caused by previously unknown agents (for example, AIDS and hantavirus pulmonary syndrome in humans, chytridiomycosis in amphibians), and those that represent the re-emergence of previously described diseases in drug-resistant or more virulent forms (for example, tuberculosis and malaria in humans, and brucellosis in cattle and wild ungulates) [39, 40].

Recent attempts to define emerging infectious disease and to classify the factors responsible for emergence in humans and wildlife have led to the description of a number of categories of causes, all of which are primarily anthropogenic in origin [39–43]. These include: (1) ecological changes, including economic development and land use, animal husbandry practices, and natural (or perhaps anthropogenic) climate changes; (2) demographics and behaviour, such as drug use, sexual behaviour, crowding, and war; (3) international travel, commerce, and movement of livestock; (4) technology, including changes in food processing, tissue transplantation, and use of immunosuppressive drugs and antibiotics; (5) microbial evolutionary change; and (6) breakdown in public health measures. These underlying causes could not have led to our current awareness of emerging infectious disease without accompanying recent improvements in disease surveillance, diagnostic capabilities, and physician awareness that have enabled the recognition of these diseases and the demonstration of their aetiologies. In fact many diseases that appear to be emerging are ‘new’ only to human awareness. Hantavirus pulmonary syndrome was only recognised in the Americas in 1993. Yet cases have now been identified retrospectively from the 1950s and molecular evidence suggests that hantaviruses and the diseases they cause have likely existed for millions years.

Many of the most dramatic emerging infections are zoonoses. The introduction of ‘new’ zoonotic diseases into populations of humans or domestic animals often

follows the incursion of humans (accompanied by their domestic animals, livestock, and crops) into remote, natural habitats where previously unknown disease organisms have existed for many years in association with wild animal hosts. Upon contact with new host species, these disease organisms may jump species barriers and 'spill-over' into populations of humans, or their crops or livestock. Zoonotic infections may be passed directly to humans from the natural reservoir, or they may be transmitted to humans via an intermediate, amplifying host. When human incursion into natural areas results in the introduction of disease into humans or their crops and livestock, additional anthropogenic factors may contribute to spread of these diseases through populations of the new host. Unlike the natural host that may have evolved with the pathogen for many years, the naïve host has no natural immunity or evolved resistance. The maintenance of monocultures of genetically similar or identical individuals eliminates the genetic resistance inherent to natural heterogeneous populations and makes all individuals equally susceptible to infection. Finally, artificially maintained population densities that far exceed the normal carrying capacity of the land facilitate the rapid spread of pathogens throughout populations.

## 8. Possible emergence factors for HeV and NiV

The period from 1994 to 1999 has seen the emergence of four previously undescribed viruses of flying foxes in the Australasian region: HeV, Australian bat lyssavirus, and Menangle virus in Australia, and NiV in Malaysia. Such a clustering of emergence in time and space is more plausibly explained by disease emergence than by chance. The identification of species of flying fox as the probable natural host of all four viruses is explained by the increased disease surveillance interest in bats that followed the identification of anti-HeV antibodies in Australian species.

The molecular characterisation and phylogenetic analysis suggest that both HeV and NiV are 'old' viruses [1, 44], very probably having remained unknown in their ecological niche over time, until factors precipitated their contact with susceptible naïve populations. Of those previously described, ecological change is the most plausible key factor in the emergence of HeV and NiV. Available data on many fruit bat species suggest that populations in Australia and southeast Asia are in decline and disruption throughout their range. Anthropogenic activities, primarily habitat loss and hunting, have been identified as constituting the major threats [30]. Deforestation, whether for agricultural land, commercial logging, or urban development, is widespread in the region and results in loss or abandonment of roosting sites, and the loss of feeding habitats. Secondly, habitat loss due to clearing is commonly exacerbated by tropical storms, the remnant forest being particularly prone to high wind damage. Hunting, whether for consumption or crop protection and at both a local and at a commercial level, results in the abandonment of roost and feeding sites. A scenario emerges of fruit bat populations under stress, of altered foraging and behavioural patterns, of

niche expansion, and of closer proximity to man. In Australia, the geographic redistribution of roosting sites has been increasingly into urban areas in recent decades (Hall L., personal communication).

Reports of apparent epidemic disease in flying fox populations date back to the 1930s, when high mortalities in colonies of *Pteropus mariannus* in Kosrae (Micronesia) were observed by local residents to be associated with an outbreak of measles in the human population. Another apparent epidemic that depleted *Pteropus tonganus* populations near Savu Savu, Fiji, was reported in 1949 [30]. More recently, in 1985 on Manus Island (north of the Papua New Guinea mainland), dead and dying *Pteropus neohibernicus* were found beneath their roosts over a period of several weeks. A similar event was observed in 1987 in populations of *Pteropus rayneri* on Bougainville and Buka (in the northern Solomon Islands) [45]. It is possible that these reports represent examples of naïve flying fox populations exposed by displaced vagrants to disease endemic in other flying fox populations.

The emergence of NiV disease provides a case study illustration of anthropogenic factors clearly contributing to three classic steps in disease emergence described by Morse [43]. The establishment of pig farms within the range of the natural host led to the initial introduction into the pig population; the maintenance of high densities of pigs led to the rapid dissemination of the infection within local pig populations; and the transport of pigs to other geographic areas for commerce led to the rapid spread of disease in pigs in southern Malaysia and Singapore. The presence of a high-density, amplifying host population facilitated transmission of the virus to humans.

## 9. Bats as a reservoir of further emerging infectious diseases

The behavioural ecology of many species of bat identifies them as potentially efficient vertebrate disseminator hosts of mammalian viruses. Sulkin and Allen [46] contend that bats are unique in their response to viral infections, in that they can sustain viral infections in the absence of overt disease. Evidence of a wide range of viral infections, including numerous arboviruses, numerous rhabdoviruses, arenaviruses, reoviruses, and paramyxoviruses have been identified in bat species [46]. The emergence of HeV and NiV represents a quantum leap in terms of the significance of bat-related viruses to human and animal health, and is of wider interest than to Australia and Malaysia. As described earlier, the distribution of the family Pteropodidae worldwide encompasses southeast Asia, the Pacific islands, India, Madagascar, and much of Africa, with flying foxes found over the entire range except Africa [30]. The overlapping ranges of neighbouring species [38] make feasible the inter-species transmission of viruses, or the possibility of related viruses in other pteropod species across the entire range.

In assessing future threats posed by zoonotic agents, Morse [43] observes that the numerous current examples of emerging infectious disease with zoonotic origins are ready evidence of the rich and apparently inexhaustible

reservoir latent in other species. He directly attributes the increased rate of emergence to the impact of primarily anthropogenic activities, and emphasises the need for effective global surveillance and rapid response, knowledge of the factors underlying disease emergence, resource focus on potential situations, and the development of more effective prevention strategies. Given that our ever-increasing population makes it improbable that anthropogenic activities contributing to emergence will decrease, these are essential goals if we are to meet the challenge of escalating disease emergence.

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