Henipaviruses: Emerging Paramyxoviruses Associated with Fruit Bats

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Abstract Two related, novel, zoonotic paramyxoviruses have been described recently. Hendra virus was first reported in horses and thence humans in Australia in 1994; Nipah virus was first reported in pigs and thence humans in Malaysia in 1998. Human cases of Nipah
virus infection, apparently unassociated with infection in livestock, have been reported in Bangladesh since 2001. Species of fruit bats (genus *Pteropus*) have been identified as natural hosts of both agents. Anthropogenic changes (habitat loss, hunting) that have impacted the population dynamics of *Pteropus* species across much of their range are hypothesised to have facilitated emergence. Current strategies for the management of henipaviruses are directed at minimising contact with the natural hosts, monitoring identified intermediate hosts, improving biosecurity on farms, and better disease recognition and diagnosis. Investigation of the emergence and ecology of henipaviruses warrants a broad, cross-disciplinary ecosystem health approach that recognises the critical linkages between human activity, ecological change, and livestock and human health.

1
Introduction

The apparent temporally clustered emergence of Hendra virus and Nipah virus in Australia and Malaysia, respectively, and the identification of species of fruit bats (*Pteropus* spp., commonly known as flying foxes) as likely reservoir hosts, poses a number of important questions on the ecology of henipaviruses. What factors precipitated their emergence? Why did they emerge at this time? What are the spillover mechanisms? What is their geographic occurrence? What are the potential impacts on humans and domestic species? The more recent description of Nipah virus-attributed disease in humans in Bangladesh reinforces the need for a comprehensive understanding of the ecology and, more broadly, epidemiology of these agents. This chapter describes the emergence of Hendra and Nipah viruses and the search for their natural hosts, discusses the impacts of emergence, and suggests factors putatively associated with emergence.

2
Emergence

2.1
Hendra Virus

Hendra virus was first described in 1994 in Australia when it caused an outbreak of severe acute respiratory disease with high mortality in thoroughbred horses in a training stable in the city of Brisbane (Murray et al. 1995b). A member of the family *Paramyxoviridae*, Hendra virus was initially called equine morbillivirus, but was later re-named Hendra virus, after the Brisbane suburb where the outbreak occurred.

To date there have been five known foci of Hendra virus infection in horses: Brisbane 1994, Mackay 1994, Cairns 1999, Cairns 2004, and Townsville 2004
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(Fig. 1). The putative index case in the Brisbane outbreak was a heavily pregnant mare at pasture. She was observed to be ill on September 7, 1994 and moved to the Hendra training facility for intensive care, but died 2 days later. Over the following 14 days, 12 of 23 thoroughbreds in the facility and a neighbouring stable became ill and died acutely or were euthanised terminally (Fig. 2) (Murray et al. 1995a). Clinical signs included fever, facial swelling, severe respiratory distress, ataxia, and terminally, copious frothy (sometimes blood-tinged) nasal discharge. There were four non-fatal cases, two of which retained mild neurological signs. A further three horses in the stable were subsequently found to have seroconverted without apparent clinical signs. All seven were subsequently euthanised (Baldock et al. 1996; Douglas et al. 1997).

The trainer and a stable hand, both directly involved in nursing the index case, became ill with a severe influenza-like illness within a week of contacting the index case. The trainer was hospitalised and subsequently died after respiratory and renal failure. Infection with Hendra virus was demonstrated in both cases (Selvey et al. 1995).

The Mackay (1994) spillover chronologically preceded the Brisbane outbreak by 5 weeks, but was only retrospectively identified in October 1995 after the Hendra virus-attributed death of a thoroughbred stud-owner suffering a...
relapsing encephalitis. Two horses were infected on the Mackay property, both fatally (Hooper et al. 1996; Rogers et al. 1996). The first horse, a 10-year-old heavily pregnant thoroughbred mare died on August 1, 1994 after exhibiting severe respiratory distress, ataxia, and marked swelling of the cheeks and supra-orbital fossa over a 24-h period. The second horse, a two-year-old colt in an adjoining paddock was reported to have licked the muzzle of 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 (Allworth et al. 1995).

Serological studies were an integral part of the outbreak investigations of the Brisbane and Mackay incidents. No evidence of Hendra virus infection was found in 800 domestic animals surveyed on the case properties or on in-contact properties. They included 387 horses, 287 cattle, goats and pigs, 23 dogs, 64 cats, and 39 poultry (Baldock et al. 1996; Rogers et al. 1996). Particular effort was directed towards surveying the broader horse population in the state of Queensland, with a further 2,024 horses from 166 properties sampled in a structured survey (Ward et al. 1996). With the exception of the seven horses that survived infection in the Hendra outbreak, none of the surveyed domestic animals showed serological evidence of exposure to Hendra virus. The negative surveillance findings (based on a highly sensitive serum neutralisation test) provided a high level of confidence that Hendra virus was not being sustained by in-contact domestic animal transmission, was not

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**Figure 2** Chronology of equine and human cases of disease attributed to Hendra virus infection in the Brisbane outbreak. (From Murray et al. 1995a)

| September 1994 |
|---------------|
| 7  9  13  14  15  16  17  19-26 |
| **Horses** |
| Cannon Hill (Paddock) | 2 horses moved |
| Hendra (Stables) | Mare died |
| Hendra (Neighboring property) | 2 horses moved |
| Kenilworth (150 km distant) | 1 horse moved |
| Samford (Paddock) | 1 horse dead |
| New South Wales |
| **Humans** |
| Stablehand | Recovered |
| Trainer | Recovered |
| | Hospitalized |
| | Died |

Specifications:
- **Cannon Hill (Paddock):** 2 horses moved.
- **Hendra (Stables):** Mare died.
- **Hendra (Neighboring property):** 2 horses moved.
- **Kenilworth (150 km distant):** 1 horse moved.
- **Samford (Paddock):** 1 horse dead.
- **New South Wales:**

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| Stablehand | Recovered |
| Trainer | Recovered |
| | Hospitalized |
| | Died |
established in the Queensland horse population, and that the outbreak was unlikely to have originated from domestic species. Because of the temporal clustering of the Mackay and Brisbane incidents, efforts were made to identify possible links between the two properties. These investigations, undertaken in late 1995, and focused primarily on horse movements, personnel movements, and management practices, found no evidence to directly link the two outbreaks.

In January 1999, a third spillover was identified in a non-pregnant mare near Cairns in north Queensland. The horse deteriorated despite symptomatic treatment and was euthanised. A companion horse was unaffected on clinical and serological examination (Field et al. 2000).

In late 2004, again in north Queensland, in two spatially and temporally clustered events in Cairns and Townsville, a further two horses (both geldings) were fatally infected and a human case non-fatally infected. The human case, a veterinarian who undertook a necropsy on the first (Cairns) horse, and two assisting handlers, reported influenza-like symptoms 8–10 days after the necropsy. All three were negative for antibodies to Hendra virus by immunofluorescent antibody test (IFT) and enzyme-linked immunosorbent assay (ELISA) at that time. A follow-up sample taken from the veterinarian was positive by IFT and ELISA, and neutralising antibodies to Hendra virus were detected by serum neutralisation test. The two handlers remained seronegative. The veterinarian made an uneventful recovery. The horse was retrospectively diagnosed as a presumptive case on clinical grounds—no samples were available for laboratory confirmation (Field et al. 2007).

2.2 Nipah Virus

2.2.1 Malaysia

A major outbreak of disease in pigs and humans occurred in peninsular Malaysia between September 1998 and April 1999, resulting in the death of 105 of 265 human cases, and the culling of over 1 million pigs (Chua et al. 1999; Nor et al. 2000). Initially attributed to Japanese encephalitis virus, the primary disease aetiology was subsequently shown to be another previously undescribed virus of the family *Paramyxoviridae*. Preliminary characterisation of an isolate at the Centers for Disease Control and Prevention in Fort Collins, Colorado, and Atlanta, Georgia, USA, showed that the new virus, subsequently named Nipah virus, had ultrastructural, antigenic, serologic and molecular similarities to Hendra virus (CDC 1999).
The epidemic primarily impacted on pig and human populations. Infection in pigs was highly contagious, and clinical disease was characterised by acute fever with respiratory and/or neurological involvement. Incubation was estimated to be 7–14 days. Crude case mortality was low (<5%), and notably, a large proportion of infected pigs was asymptomatic. The clinical course appeared to vary with age. Sows primarily presented with neurological disease, but sometimes died suddenly without evident signs. In weaners and porkers, a respiratory syndrome predominated, frequently accompanied by a harsh non-productive (loud barking) cough. 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 (Chua et al. 1999; Goh et al. 2000). The majority of human cases had a history of direct contact with live pigs. Most were adult male Chinese pig farmers (Chua et al. 1999; Parashar et al. 2000).

Evidence of Nipah virus infection was also been found in dogs, cats and horses (Chua et al. 1999; Nor et al. 2000). The initially high prevalence of infection in dogs in the endemic area during and immediately following the removal of pigs suggested that dogs readily acquired infection from infected pigs. The much lower antibody prevalence and restriction of infection to within 5 km of the endemic area suggests that Nipah virus did not spread horizontally within dog populations, and that dogs were effectively a dead-end host (Field et al. 2001).

2.2.2 Bangladesh

Five outbreaks of Nipah virus-associated disease in humans were described in Bangladesh between April 2001 and February 2005 (Anonymous 2003, 2004a, 2004b, 2005b; Hsu et al. 2004). To 11 February 2005, a total of 122 cases were recognised by the Bangladesh Directorate of Health Services, at least 78 (64%) of which were fatal. 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. However, in marked contrast to the Malaysian outbreak, infection in humans was not associated with disease in pigs (indeed pigs are uncommon in Bangladesh), and there was evidence of horizontal human transmission (discussed Sect. 4).

The first reported outbreak (13 cases, nine fatal) was in Meherpur in April–May 2001. The index case, a 33-year-old farmer, developed symptoms on April 20, and died 6 days later. Four other persons in the same household became cases 10–18 days after the index case. A further four of the cases were
relatives of the index case. The second reported outbreak of 12 cases (eight fatal) occurred in Naogaon in January 2003. The index case was a 12-year-old boy. Cases occurred in eight households. A cluster of cases occurred in one household after the head of the household became ill and later died. Two weeks later, his wife and his three eldest daughters became ill; his wife and one daughter died. In both the Meherpur and Naogaon outbreaks, handling or exposure to patient secretions was a risk factor for illness (Hsu et al. 2004).

The third reported outbreak occurred simultaneously in Goaland (Rajbari district) and seven other districts between January and February 2004. A total of 29 cases were reported, of whom 22 died. There was a predominance of young boys in the Goaland cluster, suggesting that a specific activity (such as climbing trees or ingesting fruits contaminated with the secretions of infected bats) may have led to exposure (Anonymous 2004a). The fourth reported outbreak occurred in the Faridpur district in April 2004. Of 36 identified cases, 27 were fatal. This outbreak differed from previous outbreaks in two important ways. Firstly, at least six patients developed an acute respiratory distress syndrome, in contrast to the previously observed predominant fever/neurological presentation; and secondly, the epidemiological evidence clearly indicated that person-to-person spread (possibly through large droplet transmission) was the primary mode of transmission. A fifth reported outbreak (12 cases, 11 fatal) was reported in January 2005, in the northern district of Tangail. Cases predominantly exhibited fever and neurological symptoms. Drinking raw date palm juice was the only surveyed exposure significantly associated with illness. Bats reportedly frequently drink from the open pots into which dripping juice is collected overnight, and bat excrement is reportedly common on or in the pots (Anonymous 2005b).

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 in 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 present in sequences obtained in 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); those from Bangladesh cases formed a cluster clearly distinct from the Malaysian sequences, but differed from each other by approximately 0.8%, suggesting possible multiple introductions of virus into humans. As yet, sequence data are unavailable from virus isolates obtained from putative person-to-person transmission chains to suggest genetic changes potentially associated with
adaptation to the novel human host. Sequence changes in SARS coronavirus isolated from palm civets and from humans suggest active selection of novel genotypes, including genotypes potentially adapted to a novel human reservoir host (Liu et al. 2005; Song et al. 2005). Such genetic adaptation is a significant transition point in the evolution of specific human pathogens by which agents can emerge as pandemic threats, such as HIV and influenza A subtypes (see the chapter by Childs et al., this volume; Childs 2004).

3 Reservoir Studies

3.1 Hendra Virus

The emergence of Hendra virus caused consternation for both animal and public health authorities in Australia. Zoonotic infections of horses were previously unknown, yet it quickly became evident that the infection and consequent death of the trainer was attributable to his close contact with the index horse case. When the aetiological agent was established as a novel virus of the family Paramyxoviridae, the search for its origin began. The phylogenetic analysis suggested that the virus had not resulted from single or multiple point mutations from a closely related virus, and that emergence from a natural host was the most probable explanation of its origin (Murray et al. 1995b). Serosurveillance of wild-caught wildlife, initially in the Brisbane index case paddock, and later the Mackay index case property, was undertaken to evaluate this hypothesis. Negative findings prompted broadening of the sample base to include sick and injured wildlife in temporary captivity. Apart from increasing the number of species and locations sampled, this approach offered the advantages of a convenient and cost-effective sample, and access to that subset of the greater wildlife population in sub-optimal health. Access to the latter was of particular interest, because if infection in a natural host was associated with disease or debility, then infected animals would be over-represented in this group and thus more readily detected. Species that were common to the two locations and able to move readily between the two locations were given the highest surveillance priority (Young et al. 1996).

Flying foxes (genus Pteropus, order Chiroptera) were the only mammalian species meeting these criteria. The knowledge that viruses of the family Paramyxoviridae had previously been isolated from bats elsewhere (Henderson et al. 1995; Pavri et al. 1971) reinforced this focus. Of 27 flying foxes screened using this approach, 40% had antibodies neutralising Hendra virus (Field 2005)—a major breakthrough in the search for the origin of Hendra virus. Subsequently,
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virus was isolated from two species (Halpin et al. 2000). Investigations of the role of flying foxes in the ecology of the virus continued, and subsequent studies showed evidence of previous exposure to Hendra virus in all four mainland Australian flying fox species across their range. Species (*Pteropus alecto*) and increasing age were risk factors for infection in flying foxes. Retrospective studies identified evidence of infection in flying foxes well before the first known spillover to horses (Field 2005). These features suggest a major role for flying foxes in the ecology of Hendra virus, and are consistent a mature host-agent relationship. Subsequent studies identified neutralising antibodies to Hendra virus in multiple flying fox species in Papua New Guinea to the immediate north of Australia (Mackenzie et al. 2001). Current research priorities include modelling virus maintenance in flying fox populations (Plowright et al. 2005) and defining flying fox population dynamics by genetic and satellite telemetry studies (Daszak et al. 2006).

3.2 Nipah Virus

Investigation of the origin of Nipah virus was an integral part of the Malaysian outbreak response, 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. Molecular and serologic evidence indicating that Nipah and Hendra viruses were closely related made Malaysian bat species a logical surveillance priority. Malaysia has a great diversity of bat species: at least 13 described species of fruit bat (sub-order *Megachiroptera*), including two flying fox species, and 60 described species of insectivorous bats (sub-order *Microchiroptera*) in peninsular Malaysia alone (Medway 1978). Wildlife rescue networks are less extensive in Malaysia than in Australia, thus an opportunistic sampling methodology was not a realistic option in the Nipah virus investigations, as it was in Australia with Hendra virus, and wild-caught bats were the primary survey target. Over a 5-week period, bat populations at multiple locations across peninsular Malaysia were sampled, with sampling locations including but not limited to the outbreak areas. Neutralising antibodies to Nipah virus were found in bats from five species, but predominantly in *Pteropus hypomelanus* and *Pteropus vampyrus* (Johara et al. 2001). Subsequently, Chua et al. (2002) recovered Nipah virus from the urine of *P. hypomelanus* and from partially eaten fruit which had been contaminated by bat saliva or, less likely, bat urine. Current research priorities include investigation of the population dynamics of *P. vampyrus* in Malaysia and across its range, and the dynamics of Nipah virus infection in *P. vampyrus* and *P. hypomelanus* (Daszak 2005).

Ubiquitous peridomestic species were also extensively surveyed in seeking the origin of Nipah virus in Malaysia. The uniformly negative serology results
from surveyed peridomestic rodents, insectivores, and birds in Malaysia (Asiah et al., unpublished data) indicate that these animals did not play a role as secondary reservoirs for Nipah virus. However, dogs did readily acquire infection following close association with infected pigs, and while horizontal transmission was not evident in dog populations, infected dogs possibly played a role in farm-to-farm transmission.

A serologic survey of domestic and wild animals undertaken after the 2001 Meherpur and 2003 Naogaon outbreaks in Bangladesh identified evidence of infection only in the flying fox *Pteropus giganteus*. Other (unidentified) bats showed no evidence of infection (Anonymous 2004a; Hsu et al. 2004). Concurrent serologic surveillance of *P. giganteus* in India in 2003 found that 54% had neutralising antibodies to Nipah virus (Epstein et al., unpublished observations), suggesting that Nipah virus or a cross-neutralising virus was widespread across the range of *P. giganteus*. Further, identification of neutralising antibodies to Nipah virus in *P. vampyrus* in Indonesia (Sendow et al. 2005) and Cambodia (Olson et al. 2002), and the isolation of Nipah virus from flying foxes in Cambodia (Reynes et al. 2005) strongly supported the hypothesis of Halpin et al. (2000) that henipaviruses likely exist across the entire global distribution of pteropid bats. A comprehensive investigation of the ecology of NiV in *P. giganteus* is needed to underpin risk management strategies in Bangladesh. Obvious research priorities include population dynamics of *P. giganteus*, Nipah virus infection dynamics in the species, potential modes of transmission to humans, and identification of factors precipitating emergence.

4 Modes of Spillover Transmissions

4.1 Hendra Virus

The mode of transmission of Hendra virus infection to horses in Australia has yet to be established. However, epidemiological investigations of natural infections in horses and flying foxes, and the outcomes of experimental infections in a range of species, provide useful information. Firstly, respiratory spread has not been demonstrated experimentally in any species, and the spatial pattern in naturally infected horses has not been consistent with respiratory spread. Secondly, Hendra virus has been isolated from the kidney and urine of horses and cats experimentally infected with Hendra virus, and cat-to-cat transmission and suspected cat-to-horse transmission have been attributed to exposure to
infected urine (Westbury et al. 1996; Williamson et al. 1998). Thirdly, horses have been experimentally infected by the naso-oral route (Williamson et al. 1998).

Thus, hypotheses involving (1) the excretion of an infective dose of Hendra virus from a flying fox, (2) contamination of pasture, and (3) ingestion of the contaminated pasture by a susceptible horse are plausible. Young et al. (1997) proposed that transmission from flying foxes to horses was effected by contact with infected foetal tissues or fluids via the ingestion of recently contaminated pasture. This hypothesis was largely based on the August–September temporal overlay of the Brisbane and Mackay spillovers with the late gestation of P. alecto and P. poliocephalus in Queensland, the isolation of the virus from uterine fluid and foetal tissues of a naturally infected pregnant flying fox (Halpin et al. 2000), and on the absence of evidence of infection in flying fox carers regularly exposed to other potential routes of excretion such as urine, faeces and oro-nasal secretions.

Notwithstanding the latter, an alternative hypothesis is that the ingestion of pasture contaminated with infected flying fox urine is the mode of transmission to horses. Although Hendra virus has yet to be isolated from flying fox urine, the previously described isolation of Nipah virus from the urine of free-living P. hypomelanus (Chua et al. 2002) supports urine as a plausible route of excretion for Hendra virus. The urine hypothesis is also supported by the experimental studies described above that attribute cat-to-cat and probable cat-to-horse transmission to exposure to infected urine. Another plausible hypothesis is that the ingestion of spats (the fibrous remains of masticated fruit dropped by feeding flying foxes) is the mode of transmission to horses. The quantity of these spats under food trees bearing fibrous fruit (such as the Ficus species present in the Brisbane index case paddock) can be substantial, and they may represent an attractive source of salivladen virus to grazing horses. The viability of virus in spats is also likely to be prolonged due to slowed desiccation, heat and ultraviolet action. Hendra virus has been isolated from the oral cavity of experimentally infected horses (Williamson et al. 1998) and as previously noted, the closely related Nipah virus has been isolated from fruit partially eaten by bats (Chua et al. 2002), supporting saliva as a plausible route of excretion of Hendra virus from flying foxes.

It should be recognised that the mode of transmission between flying foxes and the mode of transmission from flying foxes to horses may differ. The infectious dose, the routes of infection, and the physiological risk factors for infection in both species are unknown or incompletely understood. Managing the risk of spillover to horses is further constrained by the lack
of knowledge of the incidence of infection and the temporal pattern of infection (and thus excretion) in flying foxes. Regardless of the mode of transmission to horses, it is evident from natural infections and experimental studies that horse-to-horse transmission is not readily effected. The apparent exception is the first recognised outbreak in the Brisbane stables that involved 20 equine cases. However, the temporal pattern of infection in this outbreak suggests that the index case was the source of infection for all cases and that no secondary infection occurred (Baldock et al. 1996). Indeed, it is probable that horse-to-horse transmission in this instance was inadvertently facilitated by husbandry practices or other actions in the stable that resulted in the direct transmission of infected body fluids. Two plausible scenarios have been proposed: that a common syringe and needle was used to administer medication to the index case and to other (subsequently infected) horses; or that a cloth, bridle or other piece of equipment contaminated with infectious oral secretions from one horse was used on other (subsequently infected) horses. Likewise it is evident that horse-to-human transmission does not readily occur. Many people were potentially exposed to infection in the investigation of the Brisbane outbreak in particular, yet only the trainer and a strapper succumbed: both were closely involved in nursing the index case. It is also evident that bat-to-human transmission does not readily occur. After the identification of flying foxes as the origin of Hendra virus, a serologic survey of persons with high occupational or recreational exposure to flying foxes found none of 149 had neutralising antibodies to Hendra virus (Selvey et al. 1995). Whether the apparently low infectivity for horses and humans is a reflection of the innate infectivity of Hendra virus, the instability of the virus outside the host, or of ineffective contact is unclear, although experimental studies support the former.

4.2 Nipah Virus

The putative mode of transmission of Nipah virus in Malaysia is from flying foxes to pigs to humans. The epidemiological evidence indicates that the spill-over from flying foxes to pigs occurred in northern peninsular Malaysia (Nor et al. 2000). Chua et al. (2002), having isolated Nipah virus from flying fox urine and from fruit partially eaten and discarded by flying foxes, hypothesised that transmission to pigs was effected by infected flying foxes feeding in trees overhanging pig pens. Epidemiological (Nor et al. 2000) and experimental (Middleton et al. 2002) findings indicate that pigs are highly susceptible to infection, and thus once infection is introduced to a farm, on-farm spread is rapid. The primary mode of on-farm transmission was believed to be via
the oro-nasal route; the primary means of spread between farms and between regions was the movement of pigs. Secondary modes of transmission between farms within localised farming communities may have included roaming infected dogs and cats, and sharing of boar semen (although at present, virus has not been identified in porcine semen). Trucks transporting pigs may also have introduced the virus onto farms (Nor et al. 2000).

While the timing of the spillover (or spillovers) from flying foxes to pigs and the early epidemiology of infection in pig farms in northern peninsular Malaysia are unclear, retrospective investigations suggest that Nipah virus has been responsible for sporadic disease in pigs in peninsular Malaysia since late 1996. It is suggested that the disease was not recognised as a new syndrome because the clinical signs were not markedly different from those of several endemic pig diseases, and because morbidity and mortality were not remarkable (Bunning et al. 2000). Epidemiological modelling also supports an earlier spillover event (Daszak et al. 2006). They contend that a second introduction of infection was likely necessary for infection to become endemic in the 30,000-pig index-case farm and thus provide a sustained reservoir of Nipah virus from which to infect other farms.

Conclusive evidence of person-to-person transmission of Nipah virus was not found during investigations in Malaysia and Singapore. However, it should be noted that excretion of Nipah virus in urine and mucous obtained by throat swabs was readily demonstrable by isolation of virus from clinical samples obtained from acutely infected humans (Chua et al. 2001a). These data suggest the potential for person-to-person transmission of Nipah virus in southeastern Asia was epidemiologically plausible.

The evident horizontal human infection and the apparent absence of an intermediate domestic animal reservoir in the Bangladesh outbreaks are disturbing epidemiologic features not evident in Malaysia and Singapore. The earlier Bangladesh outbreaks suggested that close contact (handling or exposure to patient secretions) was necessary for person-to-person transmission, but the appearance of an acute respiratory syndrome in the 2004 Faridpur outbreak flagged the potential for much more efficient transmission. However, to date, person-to-person transmission appears to have been limited to a single generation, and no cases of transmission from patients to healthcare workers have been reported.

5 Putative Risk Factors for Emergence

A number of authors contend that a series of commonly occurring anthropogenic environmental changes drives disease emergence by pushing pathogens outside their normal population parameters (Krause 1992;
Lederberg et al. 1992; Morse 1995; Smolinski et al. 2003). They argue that the introduction of pathogens via global air travel and trade, the encroachment of human activities into wilderness regions, urbanisation, climatic changes and agricultural intensification are common drivers of emergence. For zoonotic diseases associated with wildlife reservoirs, anthropogenic factors that alter wildlife population structure, migration patterns and behaviour may also drive emergence of disease in human populations (Daszak et al. 2000, 2001). For example, human population encroachment into wildlife habitat may increase the risk of Lyme disease and other tick-borne encephalitides by driving the loss of less competent reservoir hosts and promoting a more efficient one, namely the white-footed mouse, *Peromyscus leucopus* (Ostfeld and Keesing 2000). Likewise, the introduction of a “new” infection into a human or domestic animal population may follow the incursion of humans (accompanied by their domestic animals) into previously remote natural habitats where unknown disease agents exist in harmony with wild reservoir hosts. Upon contact with new species, an agent may jump species barriers, thereby spilling over into humans or livestock. Unlike the natural host, the new host may have no natural immunity or evolved resistance. Additionally, high population densities and management practices may facilitate the rapid spread of pathogens throughout livestock populations. Infection may be transmitted to humans directly from the natural host or via an intermediate host.

The available evidence suggests that Hendra and Nipah viruses are phylogenetically distinct from other members of the *Paramyxoviridae* (Gould 1996; Murray et al. 1995b), well adapted to their natural flying fox hosts, and in whose populations they have long circulated (Field et al. 2001). The close phylogenetic relationship between Hendra and Nipah suggests a common progenitor. However, it also appears that flying fox populations in Australia and Malaysia have been separate for a length of time sufficient for the respective viruses to evolve further in geographic isolation. So what precipitated their emergence? Can environmental factors be identified that altered flying fox ecology and facilitated the movement of henipaviruses (and other bat-associated zoonoses) (Breed et al. 2005) beyond their natural ecological niche, precipitating their emergence? Disease emergence requires, in addition to the presence of an agent, an effective bridge from the natural host to a susceptible spillover host. Such bridges result from anthropogenic or natural changes to the agent, the host, or the environment. Available data on many fruit bat species suggests that populations in Australia and Asia are in decline and disruption throughout their range. In South-East Asia, anthropogenic activities (primarily habitat loss and hunting) have been identified as constituting the 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. Secondly, habitat loss due to clearing is commonly exacerbated by tropical storms, the remnant forest being particularly prone to high wind damage (Mickleburg et al. 1992). Hunting, whether for consumption or crop protection, and at both a local and a commercial level, results in the abandonment of roost and feeding sites (Mickleburg et al. 1992). A scenario emerges of bat populations under stress, of altered foraging and behavioural patterns, of niche expansion, and of closer proximity to man. In eastern Australia, the increasing urban presence of flying foxes [thought to be due to more reliable and abundant food resources (Parry-Jones and Augee 2001)] and the associated changes in flying fox population dynamics, represents a similar emergence-promoting scenario for Hendra virus.

The emergence of Nipah virus disease clearly illustrates the two-step process described by Morse (1995). The establishment of pig farms within the range of the natural host supported the initial introduction into the pig population; the maintenance of high densities of pigs and the transport of pigs led to the establishment and rapid dissemination of infection within the pig population in peninsular Malaysia. Amplification of virus within pig populations then facilitated transmission to humans. A combination of factors likely increased the opportunity for effective contact between flying foxes and pigs, and thus the initial introduction of infection into the pig population. Plausible hypotheses include:

- The unsustainable hunting of *Pteropus* bat species has caused 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 so an increased probability of effective contact and spillover.
- Regional deforestation has changed the seasonal foraging movements of *Pteropus* bats and lead to an increased reliance on horticultural crops, resulting in a relative increased density of bats proximate to human and livestock populations. (Climatic changes, forest fires and associated haze events have similarly been hypothesised to influence flying fox movement patterns (Chua 2003).
- 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 probability has been further increased by the practice of planting fruit orchards immediately adjacent to piggeries (Daszak et al. 2006).
Worldwide, there are approximately 60 species of bats in the genus *Pteropus* (family *Pteropodidae*, sub-order *Megachiroptera*). Their distribution extends from the west Indian Ocean islands of Mauritius, Madagascar and Comoro, along the sub-Himalayan region of Pakistan and India, through southeast Asia, the Philippines, Indonesia, New Guinea, southwest Pacific Islands as far east as the Cook Islands, and Australia (Fig. 3). Although other genera of *Pteropodidae* are present on mainland Africa (i.e. *Eidolon, Hypsignathus, Rousettus*, etc.) and in Asia (i.e. *Rousettus*), the genus *Pteropus* is restricted to Madagascar and surrounding islands in Africa; megachiropterans are absent from Europe and the Americas. Three of the four species of flying foxes found on mainland Australia are also found outside Australia. Black flying foxes (*P. alecto*), spectacled flying foxes (*P. conspicillatus*) and little red flying foxes (*P. scapulatus*) also occur in New Guinea, with the regional distribution of *P. alecto* extending to the Indonesian islands of Sulawesi, Lombok, Kangean and Baeween, and *P. conspicillatus* extending to the Indonesian island of Halmahera (Hall and Richards 2000; Mickleburg et al. 1992; Nowak 1994). Thus the distributions of two Australian species overlap with those of the island flying fox (*P. hypomelanus*) and the Malayan flying fox (*P. vampyrus*) in New Guinea and Indonesia. These species, at the northern extent of their range, overlap the Indian flying fox (*P. giganteus*), whose distribution extends eastward from Thailand and Burma across to India and Pakistan. Where distributions overlap, roosting camps are commonly shared. Such a scenario would facilitate the transmission of infectious agents between neighbouring species, leading to the plausible existence of related viruses in flying fox populations across their range, as previously hypothesised (Daszak et al. 2000; Halpin et al. 2000). Based

![Fig. 3 World distribution of flying foxes (genus *Pteropus*). (From Hall and Richards 2000)](image-url)
on maximum species diversity, flying foxes are believed to have originated from Sulawesi and eastern New Guinea (to the north of Australia) and to have radiated to their present distribution (Hall and Richards 2000; Mickleburg et al. 1992; Nowak 1994). Thus, by extension, if henipaviruses have co-evolved with flying foxes, it is likely that they exist across their entire geographic distribution. This hypothesis could readily be tested by screening long-isolated populations from the western extent of the global pteropid range.

6 Reservoir Management Strategies

Host management strategies have been discussed by the authors elsewhere (Mackenzie et al. 2003; Field et al. 2004). 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 and industry support (see the chapter by Childs, this volume). Broadly, current strategies for the management of henipaviruses are directed at minimising direct or indirect contact with the natural host, monitoring intermediate hosts, improving biosecurity on farms, and better disease recognition and diagnosis.

The sporadic (and apparently rare) nature of Hendra virus spillover events from flying foxes to horses, the low infectivity for horses (and consequently the 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 for flying foxes. Quarantine of infected premises, movement controls on stock, and disinfection have proved effective strategies (Baldock et al. 1996). A Hendra virus vaccine is not currently available and development of one is not foreseen. Australian veterinarians have a high awareness of Hendra virus, and Hendra virus exclusion is routinely undertaken for horses exhibiting an acute respiratory syndrome. Veterinarians involved in these disease investigations 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 have been previously proposed – breed (thoroughbred), sex (female), age (>8 years), pregnancy status (late pregnancy), housing (paddocked), season (late gestation or the birthing season of local flying foxes), and the presence of favoured flying fox food trees in the index case paddock (Field et al. 2000). In the two 2004 cases, the putative association with age, paddock status, season and flying fox
A considerable research focus on the ecology of Hendra virus has 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 strong contrast to Hendra virus, the Nipah virus outbreak in peninsular Malaysia in 1999 had an enormous economic and social impact. 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. The extensive post-outbreak surveillance program in Malaysia showed that farms that did not receive pigs 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. Horizontal transmission was not a feature of infection in humans (although the potential for person-to-person transmission was noted previously). 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 is the implementation of sound farm management practices, such as monitoring herd health and early recognition of disease syndromes. The latter includes maintaining the high level of farmer and veterinarian awareness of the disease generated by the outbreak. A second key strategy is the strict application of farm-gate biosecurity (Daniels 2000), with clearly defined protocols for the introduction of new stock. These may include quarantine and/or exclusion testing. A Nipah virus vaccine is not currently available and development of one is unlikely in the near future. Overarching the above is a strategy of advanced planning for emergency management of disease outbreaks. This involves established surveillance, detection, and emergency response capabilities. The pre-existence of the latter in Malaysia enabled the implementation of effective quarantine, movement controls, and culling to bring the outbreak under control. The Malaysian pig population is now free of Nipah virus infection.

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 orchards and other favoured flying fox food trees 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, faeces or spats, or with partially eaten fruit) can be avoided by ensuring roof run-off does not enter pig pens (Chua 2003). The emergence (or detection) of apparently directly transmitted infection
from the natural reservoir to humans and subsequent person-to-person trans-
mission (as appears to be the case in Bangladesh) presents a new and formi-
dable risk management challenge.

7 Phylogeny of Henipaviruses

Initial ultrastructural studies (Hyatt and Selleck 1996; Murray et al. 1995b) indi-
cated that Hendra virus was a member of the family *Paramyxoviridae*, possibly
genus *Paramyxovirus* or *Morbillivirus*. Comparative sequence analyses by PCR
of a portion of the matrix protein supported this, with phylogenetic analysis
indicating that the virus was distantly related to other known morbilliviruses
(Murray et al. 1995b). Hence the name equine morbillivirus was tentatively
ascribed to the virus. Subsequently the natural hosts of the virus were shown to
be flying foxes (*Pteropus* spp.) rather than horses, and sequencing of the entire
genome identified significant differences from morbilliviruses (including a
larger genome size) that supported the creation of a new genus (Wang et al.
2000). The authors proposed *Henipavirus* as the new genus, with Hendra virus
the type species and Nipah virus the second member. This was later accepted by
the International Committee for the Taxonomy of Viruses.

Several other previously unknown members of the family *Paramyxoviridae*
have been described in recent years. These include Phocine distemper virus and
Cetacean morbillivirus (genus *Morbillivirus*), responsible for disease epidemics
in marine mammals (Osterhaus et al. 1990; Taubenberger et al. 1996); Menangle
virus (genus *Rubulavirus*), which caused severe reproductive disease in a com-
mmercial piggery in Australia in 1997 (Philbey et al. 1998); Salem virus (unclas-
sified), possibly associated with a disease outbreak in horses in New Hampshire
and Massachusetts, USA in 1992 (Renshaw et al. 2000); Tupaia paramyxovirus
(unclassified), isolated from an apparently healthy tree shrew (*Tupaia belangeri*)
in Thailand (Tidona et al. 1999); Tioman virus (genus *Rubulavirus*) and Palau
virus (unclassified) isolated from flying foxes in Malaysia during attempts to
isolate Nipah virus (Chua et al. 2001b). Tioman and Menangle are phylogeneti-
cally closely related. Tupaia virus and Salem virus both share some sequence
homology with Hendra and Nipah, yet have features that preclude their inclu-
sion as henipaviruses or as morbilliviruses. While Palau virus has yet to be fully
characterised, it too appears not to fit readily into either genus. Figure 4 pres-
ents a phylogenetic representation of the family *Paramyxoviridae*.

There are two reports of isolations of paramyxoviruses from bats prior to
the description of Hendra virus in flying foxes in 1996; a sub-type of parain-
fluenza virus type 2 from *Roussettus leschenaulti* in India (Pavri et al. 1971) and
Mapuera virus from *Sturnira lilium* in Brazil (Henderson et al. 1995). Both of these viruses belong to the genus *Rubulavirus* (though unrelated to Menangle and Tioman viruses); the bat genera *Rousettus* (sub-order Megachiroptera) and *Sturnia* (sub-order Microchiroptera) are not closely related to flying foxes. A search for the ancestors of henipaviruses might best target bat species taxonomically closer to the genus *Pteropus*.

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**Fig. 4** A phylogenetic representation of the family *Paramyxoviridae*. 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. (From Chua et al. 2002)
8
An Ecosystem Health Approach

Changes in biodiversity due to human activities were more rapid in the past 50 years than at any time in human history, and the drivers of change that cause biodiversity loss and lead to changes in ecosystem services are either steady, show no evidence of declining over time, or are increasing in intensity. Under the four plausible future scenarios developed by the Millennium Ecosystem Assessment Report (Anonymous 2005a), these rates of change in biodiversity are projected to continue or to accelerate.

There is increasing realisation of the interconnectedness of the ecosystem and human health, and the relationship between the environment, human and non-human hosts, and pathogens. Daszak et al. (2000) argue that most emerging diseases exist within a finely balanced host–agent continuum between wildlife, domestic animal and human populations. Taylor et al. (2001), in examining risk factors for disease emergence, conclude that emerging diseases are three times more likely to be associated with zoonotic pathogens than with non-zoonotic pathogens. An ecosystem health approach recognises the critical linkages between human activity, ecological change and health, and fosters a multidisciplinary approach that considers a range of influencing factors such as medical, environmental, economic and socio-political factors. The complexity of the emergence and epidemiology of the henipaviruses warrants such a broad, cross-disciplinary ecosystem health approach if the associated mechanisms are to be understood and future risks managed.

9
Conclusion

Henipaviruses appear to have only recently emerged. Their ability to dramatically impact human and animal health, and the associated societal and economic consequences, has been clearly illustrated. Horizontal transmission of henipaviruses in humans, absent in Australia and Malaysia, appears to be an alarming feature of Nipah virus outbreaks in Bangladesh. If transmission in humans becomes efficient, the potential exists for a worst-case emergence scenario. Further, if henipaviruses, and the necessary and sufficient precipitating emergence factors exist across the distribution of all pteropid species, the emergence of further novel agents can be expected unless factors associated with emergence are addressed.
Addendum

There were two further separate equine cases of Hendra virus infection in Australia in 2006: in the south-east of Queensland (June), and in the north of the adjacent state of New South Wales (October). These cases had a number of features in common with previous index cases, including apparent spatial and temporal clustering (Field et al, 2007). In addition, a cluster of human cases of suspect Nipah virus disease was reported in the Kushtia region of eastern Bangladesh and neighbouring West Bengal (India) in April, 2007. The disease presented as an acute neurological syndrome. (Promed 28, 30 April 2007).

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