

Ecological Aspects of Hendra Virus

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Abstract Hendra virus, a novel and fatally zoonotic member of the family *Paramyxoviridae*, was first described in Australia in 1994. Periodic spillover from its natural host (fruit bats) results in catastrophic disease in horses and occasionally the subsequent infection of humans. Prior to 2011, 14 equine incidents involving seven human cases (four fatal) were recorded. The year 2011 saw a dramatic departure from the sporadic incidents of the previous 16 years, with a cluster of 18 incidents in a single 3-month period. The fundamental difference in 2011 was the total number of incidents, the geographic clustering, and the expanded geographic range. The 2011 cluster more than doubled the total number of incidents previously reported, and poses the possibility of a new HeV infection paradigm. Epidemiologic evidence suggests that compelling additional host and/or environmental factors were at play.

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1 Introduction

Hendra virus (HeV) was first identified at the stables of laconic racehorse trainer Vic Rail who a few years earlier had captured the imagination of the Australian public with his champion sprinter Vo Rogue, his unorthodox training techniques, and a larger than life personality. On September 23, 1994, the Brisbane suburb of Hendra (where Rail had his training stables) was transformed; by the end of the outbreak the trainer and 13 of his horses were dead, and one of his stable-hands was recovering in hospital. The syndrome in horses was typically characterized by severe respiratory signs and high mortality. Clinical signs included fever, facial swelling, severe respiratory distress, ataxia, and terminally, copious frothy blood-tinged nasal discharge. The trainer and stable hand, both of whom were directly involved in nursing the primary case Drama Series, became ill with a severe influenza-like illness within a week. The trainer was hospitalized and subsequently died after respiratory and renal failure (Selvey et al. 1995). HeV had emerged. But the causal agent was initially unknown, and the incident sparked a major disease outbreak investigation. Within a week, scientists in Queensland and at the CSIRO Australian Animal Health Laboratory in Geelong, Victoria had detected a novel virus, subsequently shown to be a previously undescribed virus of the family *Paramyxoviridae* (Eaton et al. 2007; Murray et al. 1995). The virus was initially named equine morbillivirus (EMV), but was later renamed HeV after the Brisbane suburb where the outbreak occurred (Murray et al. 1998; Wang et al. 1998). Hypotheses as to the origin of the virus included contaminated biological products, illegal performance-enhancing substances and malicious intent. When investigations failed to support any of these scenarios, consideration was given to the possibility that the virus had emerged from a wildlife reservoir. Within 18 months, neutralizing antibodies to HeV were discovered in fruit bats of the genus *Pteropus* (commonly known as flying-foxes, Fig. 1), heralding the beginning of an enduring integrated program of research into the ecology of HeV (Field et al. 2001; Halpin et al. 2000, 2011; Young et al. 1996). There is currently no effective prevention or treatment modality for HeV infection in horses or humans, although trials of a monoclonal antibody therapeutic for human use and of a subunit vaccine for horses are currently underway (Pallister et al. 2011a, b; Bossart et al. 2009, 2011; Promed 2011).

Fig. 1 Flying-foxes are bats of the genus *Pteropus* (Order Chiroptera) that forage nocturnally on fruit and floral resources, and roost diurnally in colonies sometimes numbering in tens or hundreds of thousands. Individuals may weigh over 1 Kg and have a wingspan greater than a meter

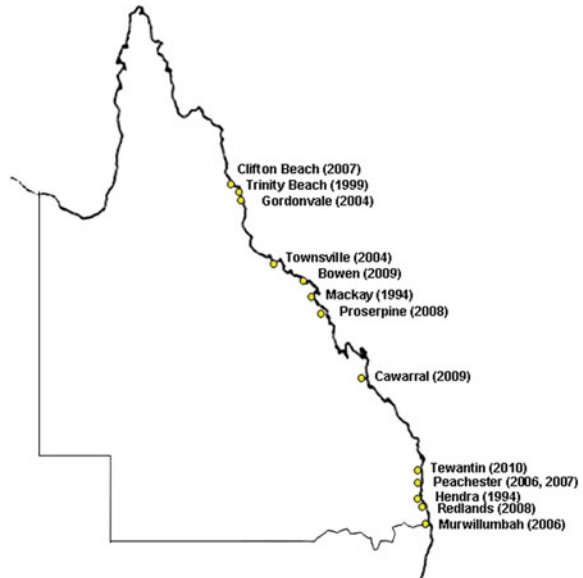


2 Hendra Virus Incidents 1994–2010

2.1 Horses and Humans

The outbreak of HeV in 1994 remains the largest single incident; subsequent incidents have involved smaller numbers of horses. While the virus is highly lethal, it has subsequently been shown to have low transmissibility, and it is believed that the large number of cases in the 1994 outbreak reflected inadvertent human-assisted transmission associated with the trainer's treatment of the sick and healthy horses. It is possible that without this single large event HeV may have remained unknown in Australia until more recent times. In the 10 years following the first HeV outbreak, a further four separate HeV incidents were recorded, all in the state of Queensland, at Mackay (1994), Cairns (1999, 2004), and Townsville (2004) (Fig. 2; Table 1). In the five years from 2006 to 2010, there was a marked increase in the frequency and number of incidents, with two incidents occurring in every year with the exception of the single incident in 2010 (Fig. 2; Table 1). These incidents were spread over a 1,500 km distance from Cairns in the far north of Queensland to Murwillumbah in the adjoining state of New South Wales. The incidents ranged from single horse events on rural properties to an outbreak in a veterinary practice involving five horses and two staff. There have been seven

Fig. 2 Locations and years of hendra virus outbreaks from 1994 to 2010



humans infected with the virus, four of whom have succumbed fatally. All human cases can be traced back to infected horses; there has been no flying-fox to human transmission, no evident transmission from flying-foxes to other species, and no human to human transmission.

2.2 Ecological Studies

Initial disease ecology studies sought to scope the ‘history’ of HeV infection in Australian flying-fox populations using serological surveillance. Field et al. (2001) found neutralizing anti-HeV antibodies in all four mainland flying-fox species (*Pteropus alecto*, *P. conspicillatus*, *P. poliocephalus*, *P. scapulatus*) across their geographic range (Fig. 3), and in archived samples that predated the first reported infection in horses. More recent disease ecology studies have focused on elaborating the spatial and temporal ‘footprint’ of virus excretion in flying-foxes, and on flying-fox-horse transmission scenarios (Field et al. 2001). HeV genome was detected by quantitative PCR in urine samples collected under roosting flying-foxes, and infectious virus isolated from a number of these samples. Although experimental studies had not demonstrated virus excretion in flying-fox urine and consequently not demonstrated experimental flying-fox to horse transmission (Williamson et al. 1998), the repeated isolation of virus from under flying-fox roosts suggests that the experimental model was flawed, and indicates that the screening of urine and other samples under roosting and foraging flying-foxes is a robust mechanism for monitoring natural infection and excretion. As part of a 3 year

Table 1 Hendra virus incidents 1994–2010

Date	Location	Horses cases (fatal cases)	Humans cases (fatal cases)
1994 August	Mackay, QLD	2(2)	1(1)
1994 September	Hendra, QLD	20(13)	2(1)
1999 January	Trinity Beach (Cairns), QLD	1(1)	0(0)
2004 October	Gordonvale (Cairns), QLD	1(1)	1(0)
2004 December	Townsville, QLD	1(1)	0(0)
2006 June	Peachester, QLD	1(1)	0(0)
2006 October	Murwillumbah, NSW	1(1)	0(0)
2007 June	Peachester, QLD	1(1)	0(0)
2007 July	Clifton Beach (Cairns), QLD	1(1)	0(0)
2008 July	Redlands, QLD	5(4)	2(1)
2008 July	Proserpine, QLD	3(2)	0/0
2009 July	Cawarral, QLD	4(3)	1(0)
2009 September	Bowen, QLD	2	0(0)
2010 May	Tewantin, QLD	1	0(0)
Total	14 events	45(31)	7(4)

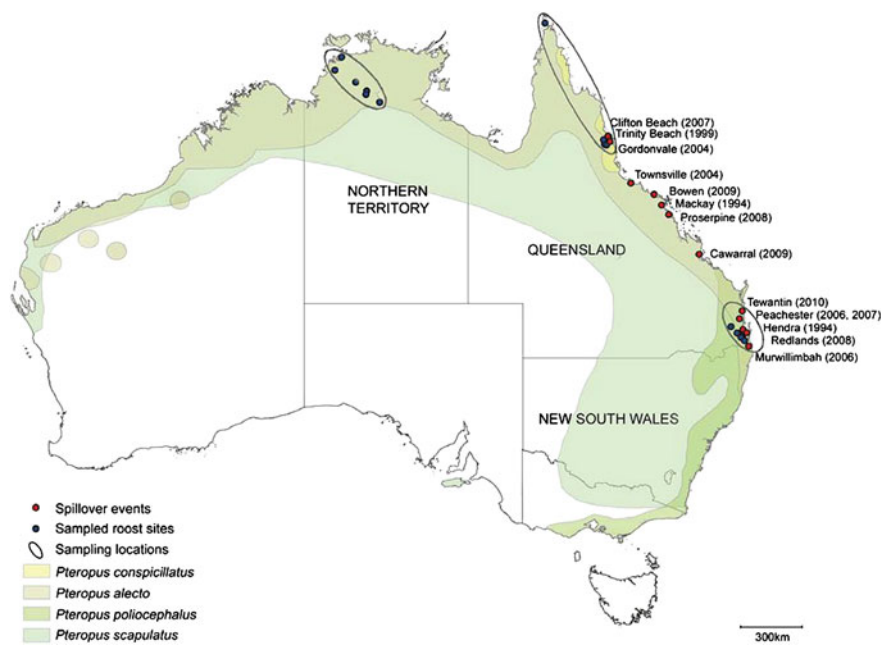


Fig. 3 The geographic range of the four mainland flying-fox species in Australia, and hendra virus antibody prevalence in the various Australian states

longitudinal study, pooled urine samples were collected from plastic sheets placed under flying-fox colonies in multiple locations in Queensland and in the Northern Territory (Field et al. 2011). Sampling locations were influenced by the location of

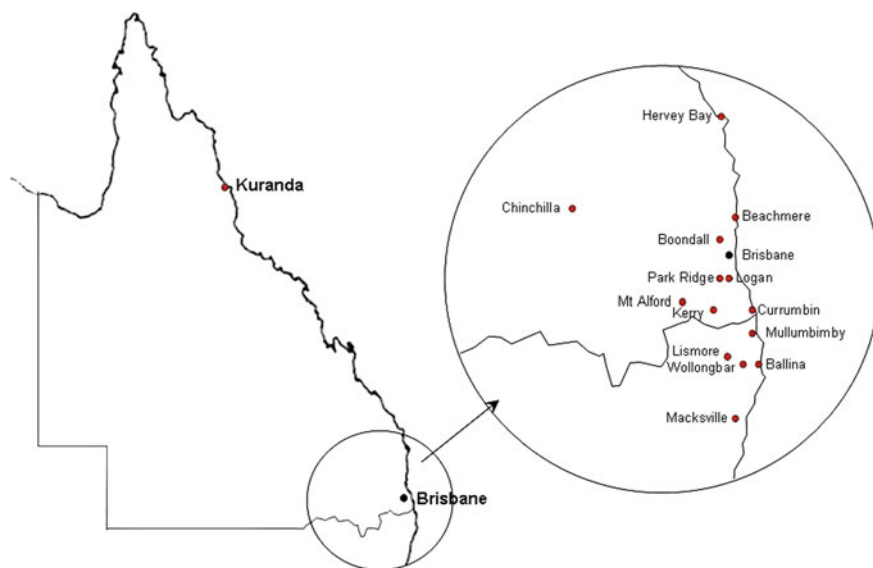


Fig. 4 Locations of hendra virus outbreaks in 2011

previous equine cases, and samples were collected on a monthly basis. Sampling locations were later expanded to include ‘real-time’ monitoring of flying-fox colonies proximate to equine cases, supporting molecular epidemiology and phylogenetic studies (Smith et al. 2011). Notwithstanding the pooled nature of the samples, the proportion of positive samples and the proportion of positive sheets provided a robust estimate of infection and excretion in the colony. In the 3 years prior to June 2011, the median proportion of positive samples from positive sampling events was 8.5%, in contrast to findings in the 3 months subsequent to June 2011 (below).

3 An Unprecedented Hendra Year 2011

3.1 *More Incidents, More Locations*

In 2011, in graphic contrast to the sporadic incidents and limited case numbers of the previous 17 years, a supercluster of 18 incidents (23 equine cases) occurred in a 12-week period in eastern Australia. Starting in late June, incidents were consecutively or simultaneously reported over a 1,800 km distance from Kuranda in far north Queensland, to Macksville in central New South Wales (Fig. 4; Table 2). Not only was the number of incidents unprecedented, but the location of the incidents extended the known southern occurrence of equine cases 300 km further south, and dramatically increased the number and proportion of incidents occurring in

Table 2 Hendra virus incidents in 2011

Date	Location	Horses cases (fatal cases)	Human cases (fatal cases)
June	Kerry, QLD	1(1)	0(0)
	Wollongbar, NSW	2(2)	0(0)
	Macksville, NSW	1(1)	0(0)
	Mt Alford, QLD	3(3)	0(0)
July	Park Ridge, QLD	1(1)	0(0)
	Kuranda, QLD	1(1)	0(0)
	Hervey Bay, QLD	1(1)	0(0)
	Boondall, QLD	1(1)	0(0)
	Lismore, NSW	1(1)	0(0)
	Logan, QLD	1(1)	0(0)
	Chinchilla, QLD	1(1)	0(0)
	Mullumbimby, NSW	1(1)	0(0)
	Ballina, NSW	1(1)	0(0)
	South Ballina, NSW	2(2)	0(0)
August	Mullumbimby, NSW	1(1)	0(0)
	Curumbin, QLD	1(1)	0(0)
	North Ballina, NSW	1(1)	0(0)
	Beachmere, QLD	2(1)	0(0)
September			
Total	18 events	23(22)	0(0)

New South Wales. In addition, one Queensland incident occurred 250 km inland and on the western side of the Great Dividing Range, extending the known inland occurrence of incidents by over 200 km. In seeking to understand why 2011 was so dramatically different from the previous years (during which 9 years had two reported incidents, 2 years had one reported incident, and 9 years had no reported incidents), it is useful to examine the historic data to establish how it was different. First, incidents have previously clustered seasonally, with 9/14 (64%) incidents prior to 2011 occurring from June to September (winter and early spring in Australia). Second, incidents have previously occurred near-simultaneously in disparate geographic locations [Mackay and Brisbane (1994); Peachester and Clifton Beach (2007); Redlands and Proserpine (2008); Cawarral and Bowen (2009)]. Third, equine infection has previously been reported in NSW (1/14 pre-2011 incidents occurred in Murwillumbah 2006).

3.2 What Was Different?

What was predominantly different in 2011 was the number of incidents, the geographic clustering in southeast QLD and northern NSW, and the unprecedented number and proportion of incidents (8/18) in NSW. We propose that multiple host and environment factors drove this situation. To elaborate further, all but one of

the 18 incidents occurred within a 350 km radius of the first reported 2011 incident at Kerry, 75 km south of Brisbane. It is possible that the outlying Kuranda incident simply reflected the ‘normal’ background frequency of HeV incidents (1–2 per year), and that the drivers for the cluster of cases in south east Queensland and northern New South Wales, reflect relatively local factors. In addition, viral genome sequence from cases in horses from multiple incidents was phylogenetically consistent with that seen in previous years, strongly suggesting the 2011 cluster of incidents was not due to a new more virulent or transmissible strain of the virus, but due to nonviral factors. Finally, preliminary analysis of the pooled urine data from flying fox colonies proximate to equine cases in the 2011 cluster suggests that excretion levels were substantially higher than in the previous 3 years. The cause and relevance of this to the magnitude of the 2011 cluster is yet to be determined, as is the phylogenetic relatedness of viral genome sequence from horses and flying-foxes.

The 2011 cluster of incidents added another dimension to the history of HeV in Australia, with neutralizing antibodies to HeV detected in a dog associated with one of the equine incidents in south-east Queensland. The dog (a 2-year-old Kelpie) showed no evident clinical signs of disease, but serological testing demonstrated neutralizing anti-HeV antibodies, indicating exposure to HeV infection. The dog, from a property that had three equine cases, was subsequently euthanized. While earlier limited experimental studies had suggested that dogs could become subclinically infected, this was the first evidence of natural infection in a dog. No evidence of virus either by isolation or genetic testing was identified from the dog, precluding estimation of exposure, incubation or other epidemiological aspects. Although there is laboratory evidence of HeV infection of other species including pigs, cats, hamsters, and ferrets (Guillaume et al. 2009; Li et al. 2010; Williamson et al. 1998), and field evidence of Nipah virus infection of pigs, dogs, and horses (Chua et al. 2000), this is the first evidence of HeV infection of a species other than equine in the field. There has been no evidence of clinical signs in any other species on infected properties during current and previous incidents, and laboratory testing of ‘in-contact’ known susceptible species has not previously identified evidence of HeV infection.

The absence of human cases was a notable feature of the 2011 cluster. In the 14 reported equine incidents prior to 2011, there were 7 human cases, 4 with fatal outcomes; a horse trainer (1994), a farmer assisting a veterinarian perform a necropsy (1994), and two veterinarians (2008, 2009). Veterinarians and those assisting veterinarians represent five of the total seven human cases. In 2011, we would have mathematically expected nine human cases in the 18 equine incidents, assuming the same rate of infectivity and exposure. Genetic studies identify no change to the virus that might account for decreased infectivity, suggesting that altered exposure may be responsible for the absence of human cases. Notwithstanding the pathogenicity of HeV, horse to human transmission has historically been inefficient, with all human cases having direct and substantial contact with infectious body fluids of case horses. The absence of human cases in 2011 suggests that direct and substantial contact was not occurring, or not occurring with the

same frequency as previously. Plausible explanations for this include (individually or combined) increased veterinarian and horse owner awareness of HeV (fostered by a sustained campaign by animal and public health authorities since 2008), early consideration of HeV as a differential diagnosis (which likely increased as the number of cases and associated publicity grew), the implementation of risk-minimizing protocols and appropriate personal protective equipment in the management of suspect cases, timely submission of appropriate samples to laboratories and rapid diagnostic turnaround, and effective quarantine and movement controls on case properties.

3.3 An Effective Vaccine?

An effective vaccine for horses offers reduced risk of infection in both horses and humans. Two vaccines for horses are currently being developed. The first is a canary pox virus-based recombinant vaccine that carries the glycoprotein (G) gene of Nipah virus. Previous trials showed that this vaccine construct generates high levels of neutralizing antibody in pigs, and delivers protection against Nipah virus disease without shedding of infectious virus (Weingartl et al. 2006). An HeV version of this vaccine is currently undergoing trials to establish efficacy in generating neutralizing antibodies; it has yet to be trialled for protection efficacy in horses. The second vaccine is based on recombinantly expressed soluble versions of the HeV G glycoprotein (sG) (Pallister et al. 2011b), formulated with adjuvant as an inactivated vaccine. Various forms of this preparation have been used under laboratory conditions to induce neutralizing antibody in cats and ferrets, and to protect from disease following challenge by Hendra and Nipah viruses (McEachern et al. 2008; Mungall et al. 2006). The sG Hendra vaccine has now been formulated with a proprietary adjuvant for use in trials in horses. The preliminary data show sero-conversion of vaccinated horses, prevention of disease following exposure to an otherwise lethal HeV challenge, elimination of viral shedding, and prevention of viral replication in tissues (D. Middleton and L.-F.Wang, unpublished results). Trials into longevity of antibody level and protection are currently underway with the target date for registration for use by the horse-owning community in 2013.

4 Fruit Bats and Hendra Virus

An insight into the natural history and ecology of HeV infection in flying-foxes is useful at this point. Serologic evidence of infection occurs in all four species, and across their geographic range in Australia (Field et al. 2001). Infection is readily detected in the urine of roosting flying-foxes, is not evident in colonies continuously, but has been detected in all months of the years across colonies (Field et al. 2001). PCR-positive urine samples and flying-fox food debris have been identified

beneath flowering/fruiting trees under which horses rest, suggesting a plausible transmission pathway (C. Smith, C. de Jong, N. Kung, and H. Field, unpublished results). There is some evidence for a positive association between pregnancy and HeV status (Breed et al. 2011; Plowright et al. 2008), between ecological stress and HeV status (Plowright et al. 2008), between incident location and proximity to flying fox roost (C. Smith, C. de Jong, N. Kung, and H. Field, unpublished results), and between lower rainfall periods and HeV incidents (C. Smith et al., unpublished results).

Thus, there is support for a complex causality for HeV spillover from flying-foxes to horses. That equine incidents are seasonally clustered when virus excretion is detected year-round supports this hypothesis; although the previous occurrence of incidents outside this June to September period (October to December, January and May) underlines that spillover can occur at any time, it is more likely to occur at sometimes than others because the presence of additional factors make transmission (excretion/exposure/infection) more likely or more efficient. In epidemiologic terms, this scenario is explained by the concept of 'necessary and sufficient cause'; the virus is a necessary component (infection cannot occur without it), but the likelihood of infection is moderated by the presence or absence of multiple host and environmental factors, sometimes in complex interaction, and providing 'sufficient' cause for spillover to occur. Thus, in seeking to explain the events of 2011, we have hypothesized host factors such as physiological and immunological status, and environmental factors such as food resource availability and climatic variables as plausibly supporting an increased level of infection in flying-foxes, as well as the extended excretion of virus by flying-foxes, the prolonged survival of virus in the environment and the increased likelihood of equine exposure and infection. From our monitoring of flying-fox colonies in south-east QLD and northern NSW during this cluster of incidents, we know that multiple colonies were infected throughout the region at the time, that the prevalence of virus excretion in these colonies was higher than the previous 3-year median, and that virus excretion continued for longer than previously observed (Field et al. 2011). Simplistically, the probability of flying-fox to horse transmission depends on the presence of infection in a proximate colony at that time, the proportion of susceptible flying-foxes, and the size of the colony size (i.e. the potential viral load), plus the number and density of horses, and the management of the horses (i.e. effective contact). During the epidemiological investigation of the 2011 HeV outbreaks, it was observed that additional factors such as pasture state and horse behavior may also play a role in the probability of flying-fox to horse transmission (N. Kung et al., unpublished results).

HeV has a number of epidemiological features in common with the related Nipah virus. Nipah virus, a co-member of the genus henipavirus, was first identified in Malaysia in 1999 as the cause of an outbreak of respiratory and/or neurological disease in intensively farmed pigs and associated pig workers (Chua et al. 2000). As with HeV in Australia, species of flying fox were identified as the natural host, with Nipah virus spilling from bats to pigs, and from pigs to people (versus bats-horses-people with HeV) (Field et al. 2007; Yob et al. 2001).

Since 2001, Nipah virus has been identified as causing clusters of typically fatal human disease in India and Bangladesh (Epstein et al. 2006). In contrast to HeV in Australia, human cases in Bangladesh are not typically associated with an intermediate livestock host, but rather with indirect bat-human transmission (Gurley et al. 2007). While the ecology of Hendra and Nipah virus infection remains to be fully elaborated, the multiple host and environmental factors discussed above in relation to HeV are likely equally likely to drive Nipah virus infection and spillover dynamics. Both viruses exhibit marked spatial and temporal ‘patterns’, reinforcing the likely role of physiological, biological, ecological, and anthropogenic drivers. Nipah virus is discussed in detail in the companion chapters of this book.

5 Epilogue

The 2011 cluster of incidents has more than doubled the total number of incidents previously reported, and poses the possibility of a new HeV infection paradigm. This new paradigm does not relate to the horse-to-horse or horse-to-human infectivity of the virus (which thankfully remains low), but to the occurrence and frequency of spillover events, previously regarded as sporadic. While it is probable that the increased frequency of identification of equine hendra cases since 2004 may reflect (in part) increased awareness of horse owners and veterinarians, the epidemiologic evidence suggests that compelling additional host and/or environmental factors were at play in 2011. These factors remain unclear, and are the focus of an accelerated research program funded by the state governments of Queensland and New South Wales and the Australian federal government. Time will tell whether the supercluster of 2011 was an anomaly, or if it indeed heralded a paradigm-shift.

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