



Novel variant Hendra virus genotype 2 infection in a horse in the greater Newcastle region, New South Wales, Australia

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ABSTRACT

In October 2021, the first contemporary detection of Hendra virus genotype 2 (HeV-g2) was made by veterinary priority disease investigation in a horse near Newcastle, New South Wales, Australia, as part of routine veterinary priority disease surveillance.

This discovery followed an update of Hendra virus diagnostic assays following retrospective identification of this variant from 2015 via sentinel emerging infectious disease research, enabling timely detection of this case. The sole infected horse was euthanized in moribund condition. As the southernmost recognised HeV spill-over detection to date, it extends the southern limit of known cases by approximately 95 km. The event occurred near a large urban centre, characterised by equine populations of diverse type, husbandry, and purpose, with low HeV vaccination rates.

Urgent multi-agency outbreak response involved risk assessment and monitoring of 11 exposed people and biosecurity management of at-risk animals. No human or additional animal cases were recognised.

This One Health investigation highlights need for research on risk perception and strategic engagement to support owners confronted with the death of companion animals and potential human exposure to a high consequence virus. The location and timing of this spill-over event diverging from that established for prototype HeV (HeV-g1), highlight benefit in proactive One Health surveillance and research activities that improve understanding of dynamic transmission and spill-over risks of both HeV genotypic lineages and related but divergent emerging pathogens.

1. Background

Hendra virus (HeV), a paramyxovirus, genus *Henipavirus*, is one of Australia's foremost high consequence zoonotic diseases, having previously resulted in four deaths among seven confirmed human cases [1]. Prior to the case of equine HeV described herein, 64 spill-over events had been recognised since discovery in 1994 in Hendra, Queensland, resulting in 106 horse deaths [2,3]. *Pteropus* fruit bat species (flying-foxes; family Pteropodidae) are considered the natural reservoir for HeV

[4]. HeV spill-over from bats to horses had been detected in eastern Australia from far north Queensland to the Hunter Valley region in NSW, where flying-fox populations overlap with populations of domestic horses [3,8–10]. Neutralising antibodies have been detected in all four species of flying-foxes on mainland Australia [5], guiding initial estimation of risk to include all areas where horse populations overlapped with flying-fox habitats – regardless of species [6]. However, prevalence of viral excretion in urine (the excretion pathway most relevant for spill-over) and the locations of past detected spill-over infections of horses [3]

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indicated that black flying foxes (*Pteropus alecto*) were the primary source of recognised transmission [7].

There have been 87 PCR-confirmed and 20 additional epidemiologically suspected cases in horses, all resulting in death or euthanasia [3]. HeV infection is endotheliotropic, causing vasculitis in horses that may affect many tissues, including lung, brain, lymphoid tissues, kidneys, liver, heart and gastrointestinal tract [11]. Clinical manifestations in horses typically feature rapid onset of illness, anorexia, tachycardia, pyrexia, depression, mucous membrane congestion, and rapid clinical deterioration with either overt respiratory or nervous signs, and some cases have been found deceased [11–13].

The seven known cases of HeV infection in people were associated with direct contact with the blood, bodily fluids, or respiratory secretions of moribund or recently deceased horses [1,14]. The HeV attack rate for people exposed to potentially infectious equine body fluids has been estimated as 10% [11]. HeV infection in people has an estimated incubation period of 9–16 days and is pathologically consistent with Nipah virus infection (a closely-related *Henipavirus*, recognised as causing more than 700 human deaths in southern Asia) and HeV disease in horses [15–17]. Early manifestations of HeV are of influenza-like illness that often progresses to encephalitis, with chronic encephalitic manifestations observed among survivors [18].

Four people have died from seven confirmed with HeV infection (case fatality rate of 57%), with death of one patient attributed to multi-organ failure with interstitial pneumonia and the remainder to encephalitis [11–18]. Since 2008, a human monoclonal antibody (mAb) m102.4 has been administered as part of emergency post-exposure therapy on compassionate grounds in 16 human cases and has undergone a phase 1 trial to demonstrate safety, tolerability, and desired pharmacokinetics without antigenicity [19]. Given the lack of a registered available human vaccine, prevention of human HeV infection currently relies on prevention in horses, for which vaccination is a mainstay, consistent with a One Health approach to preventing infection of horses and people [20].

Detections of HeV-infected horses in Australia have occurred in mid-to north-eastern New South Wales and Eastern Queensland [3]. The southern limit of detected cases has progressively extended south since the initial detection in 1994. For example, in June 2019, a case in the Upper Hunter Valley of New South Wales extended the southern limit by approximately 95 km, highlighting wider geospatial risk of spill-over. This prompted increased awareness and vaccination uptake, especially among thoroughbred breeding enterprises prominent in the region [21]. The 2019 detection prompted an interagency after-action review between animal and public health authorities to ensure continued successful One Health responses to emergency zoonotic disease events [21].

In March 2021, as part of retrospective syndromic sentinel surveillance, researchers identified a novel HeV variant of samples from a horse that suffered acute fatal disease in Queensland in 2015 [22]. The novel HeV genome was sufficiently divergent (89% nucleotide identity) to fail detection by routine qPCR but exhibited sufficiently conserved transcribed amino acid sequence (92.5% amino acid identity) and protein structure (including unchanged critical binding epitopes) to be considered equivalent in susceptibility to both the available horse vaccine and human monoclonal antibody (m102.4) [22,33]. Molecular data sharing enabled comparison of this variant HeV with that detected in specimens from a grey-headed flying-fox from Adelaide (South Australia), demonstrating 99% nucleotide sequence identity, prompting rapid communication of broad geographic spill-over risk to veterinarians and horse owners [23]. This novel variant circulating as a consistent second genotypic lineage, was subsequently named Hendra virus genotype 2 (HeV-g2) [22] [20].

Retrospective molecular detections of HeV-g2 in samples from grey-headed flying-foxes and little red flying-foxes (*P. scapulatus*) submitted from Victoria, South Australia and Western Australia for *Australian bat lyssavirus* testing between 2013 and 2021 were subsequently reported [24]. Detections in urine from black flying-foxes and grey-headed flying-

foxes in Queensland and New South Wales have also been reported [25]. These further detections provide evidence that this hitherto unrecognised variant of HeV circulates as a sub-lineage across a broader distribution than previously-recognised for prototype HeV (HeV-g1) and highlights the potential risk for sporadic spill-over of HeV to horses in all regions frequented by flying-foxes, regardless of species [22–25].

While there has been no documented human infection with HeV-g2, equivalent *in vitro* and *in silico* analyses of the receptor binding proteins of both viruses [33], along with equivalent expression of key immune suppressing viral proteins (P gene proteins V, W and P), indicate that this sub-lineage is of similar zoonotic infection potential with risk of life-threatening human disease [22]. Similarly, based on highly homologous amino acid sequences across all six proteins between HeV-g1 and HeV-g2, and observed clinical disease in the horse infected with HeV-g2 as indistinguishable from HeV-g1, these two variant HeV sub-lineages are understood to be of equivalent pathogenicity in horses [12,22].

Since June 2021, real-time polymerase chain reaction (qPCR) assays able to detect both HeV genotypes have been added to animal health laboratory HeV testing algorithms around Australia [22–24].

2. Event

On the morning of 5 October 2021, the owners of an unvaccinated seven-year-old gelding noticed that the horse was anorexic. The owners recalled the horse had been somewhat inappetent the previous day but otherwise well. The gelding began circling in the early afternoon, and its rapidly deteriorating condition prompted the owners to seek urgent veterinary care.

Upon arrival, the veterinarian found the gelding ataxic and circling in the paddock. Initial clinical assessment determined obtunded demeanour (non-responsive to external stimuli), profuse sweating, severe tachycardia (100 beats per minute), mild tachypnoea (28 breaths per minute), purple mucous membranes with significant delay in capillary refill time, mydriasis (dilated pupils), and a lack of menace response. Overt respiratory distress and abnormality in volume or consistency of oronasal secretions was not observed. Rectal temperature was normal. The gelding's condition progressively deteriorated to a moribund, featuring recumbency and nystagmus, over the course of the consultation, justifying veterinary euthanasia with owner consent by lethal injection on humane grounds.

The gelding lived alone in a one-hectare paddock in a peri-urban suburb within the greater Newcastle city region of New South Wales and had not travelled within the previous three months. Other horses were maintained in neighbouring paddocks. No horses on the property had ever received HeV immunisation. The consistency of the gelding's severe and rapidly progressive neurological disease, prompted the veterinarian's judicious collection of EDTA blood specimens for state biosecurity priority disease investigation at the Elizabeth Macarthur Agricultural Institute (EMAI), including expedited HeV testing. The veterinarian informed the owners that HeV was suspected and directed them to leave the gelding's body untouched until results were finalised, in accordance with standard suspect Emergency Animal Disease biosecurity procedures [13]. The NSW Department of Primary Industries was notified. Eleven additional people visited the deceased horse overnight to express their farewells before on-site burial took place.

By midday the following day, EMAI reported that HeV-g2 RNA was detected in all samples by qPCR. Samples were negative for HeV-g1, and the HeV-g2 diagnosis was subsequently confirmed by the Australian Centre for Disease Preparedness, Geelong. This result marked the first HeV-g2 detection in equine specimens submitted for diagnostic testing since the updated routine HeV testing. Prompt subsequent whole genome sequencing of the EDTA sample, at the partnered research laboratory, revealed 99.58% similarity to the Queensland HeV-g1 detected in a horse in 2015 (Fig. 1). The case extended the southern limit of HeV detections by approximately 95 km (Fig. 2).

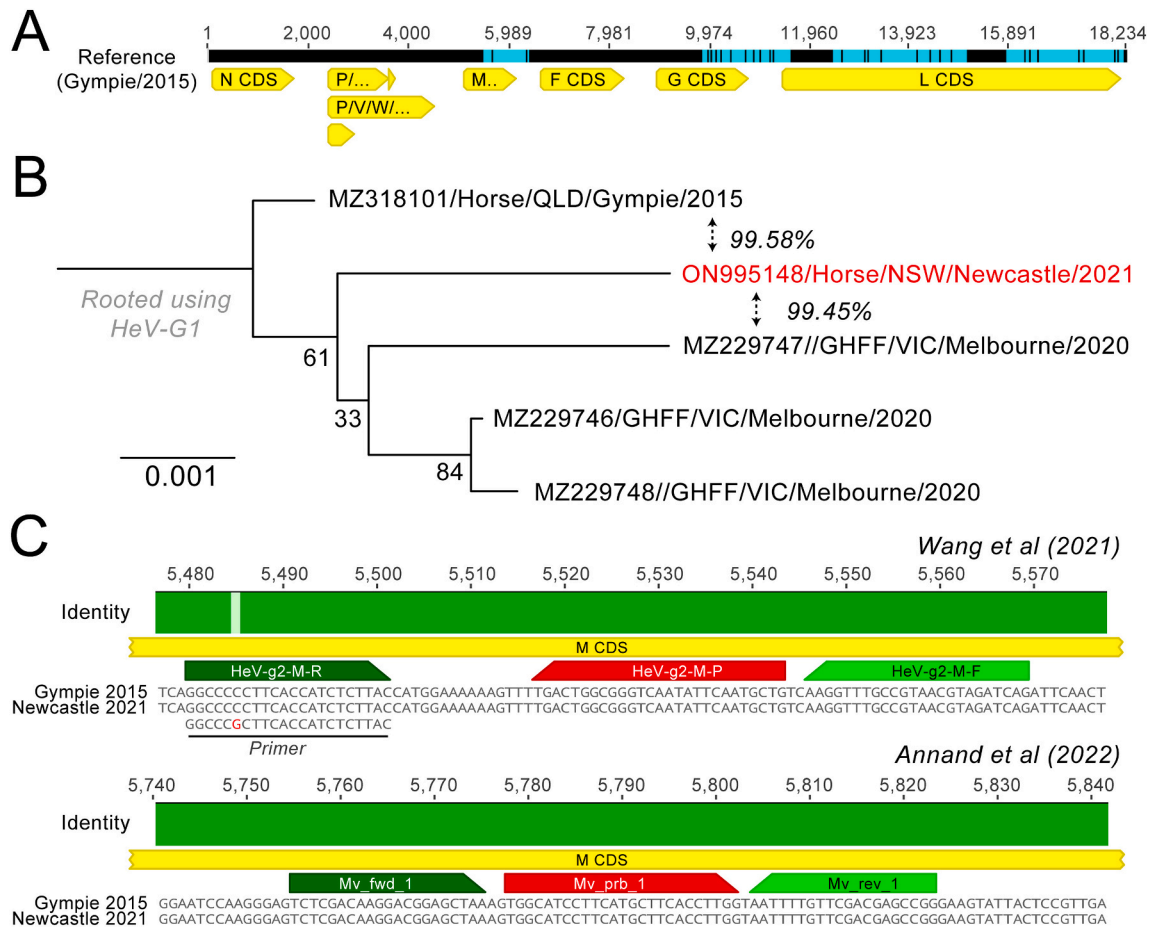


Fig. 1. Genomic sequencing of Hendra variant case in Newcastle, New South Wales in October 2021. (A) Sequencing coverage (blue coloured regions) along the Hendra variant genotype (HeVg2) horse reference genome derived from case EDTA blood RNA. (B) Maximum-likelihood Phylogenetic analysis of HeV-g2 sequences detected from horses and *grey headed flying-foxes*. Maximum-likelihood alignment was prepared for available genome sequences with the tree rooted to the prototype HeV-g1 virus. All sequences are labelled with accession number, host, state, city, and year of collection. The 2021 case is highlighted in red with arrows indicating nucleotide identity to phylogenetic neighbours. (C) Matrix gene nucleotide sequence alignment and comparison to primers and probes currently available for HeV-g2 specific real-time PCR assays were compared, identifying only a single mismatch, in a non-anchor region of the HeV-g2-M-R primer, which is not expected to impact assay performance. Otherwise, all primers and probes share 100% identity to the available HeV-g2 genomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Response

An urgent One Health coordinated response followed, with human and animal health investigations and actions commenced immediately upon laboratory confirmation of the HeV-g2 infection, with ecological investigations commencing soon after.

On 7 October 2021, a site visit was conducted by the regional district veterinarian, and a Biosecurity directions were implemented including preventing animal movement on and off the property. Epidemiologically relevant history was elicited via interviews with the owners and land-owners of neighbouring properties. Prioritised testing for HeV had been undertaken previously (7 March 2016) on samples from two horses that died suddenly while kept on the property in the same paddock. Neither of these horses had been observed for at least four days prior to finding their carcasses, and overt respiratory secretions consistent with pneumotropic HeV infection had not been evident at the time of sampling. At the time, qPCR testing (targeting HeV-g1) was negative and a causative diagnosis was not established. Unfortunately, samples from these cases were not archived, precluding the possibility of retrospective HeV-g2 testing.

Contact tracing in the present case identified nine horses with potential contact to the infected horse. These included neighbouring horses with potential direct over-the-fence contact and a horse kept further up

the road that had nose-to-nose contact with the infected horse on October 5 when it was ridden past. None of these horses were immunised against HeV. Personal-protective-equipment supplies and infection control training were provided to their owners to minimise subsequent risk. The health of these horses was monitored closely by their owners for 21 days.

Hunter New England Public Health Unit (HNEPHU) conducted contact tracing and interviews with 12 people perceived as potentially exposed to the infected horse. Human health risks were assessed based on consideration of these data by a Hendra Expert Panel consisting of human and animal health infectious disease and public health experts. Contacts were assessed as having low-moderate ($n = 3$), low ($n = 8$), negligible ($n = 0$) or nil ($n = 1$) likelihood of transmissible exposure. Indication for post-exposure therapy with mAb m102.4 was not determined, in the context of administration as an unlicensed medicine being limited to confirmed or highest risk infection scenarios on compassionate grounds [26]. The single relatively minimal respiratory disease manifestation (mild tachypnoea) in the infected horse influenced the panel's assessment of potential transmissible human exposures. Higher transmissible exposure risk was assessed for several contacts who interacted closely with the carcass during farewell and grieving processes, (at odds with veterinary biosecurity instruction) involving increased likelihood of close oro-naso-facial contact with the infected

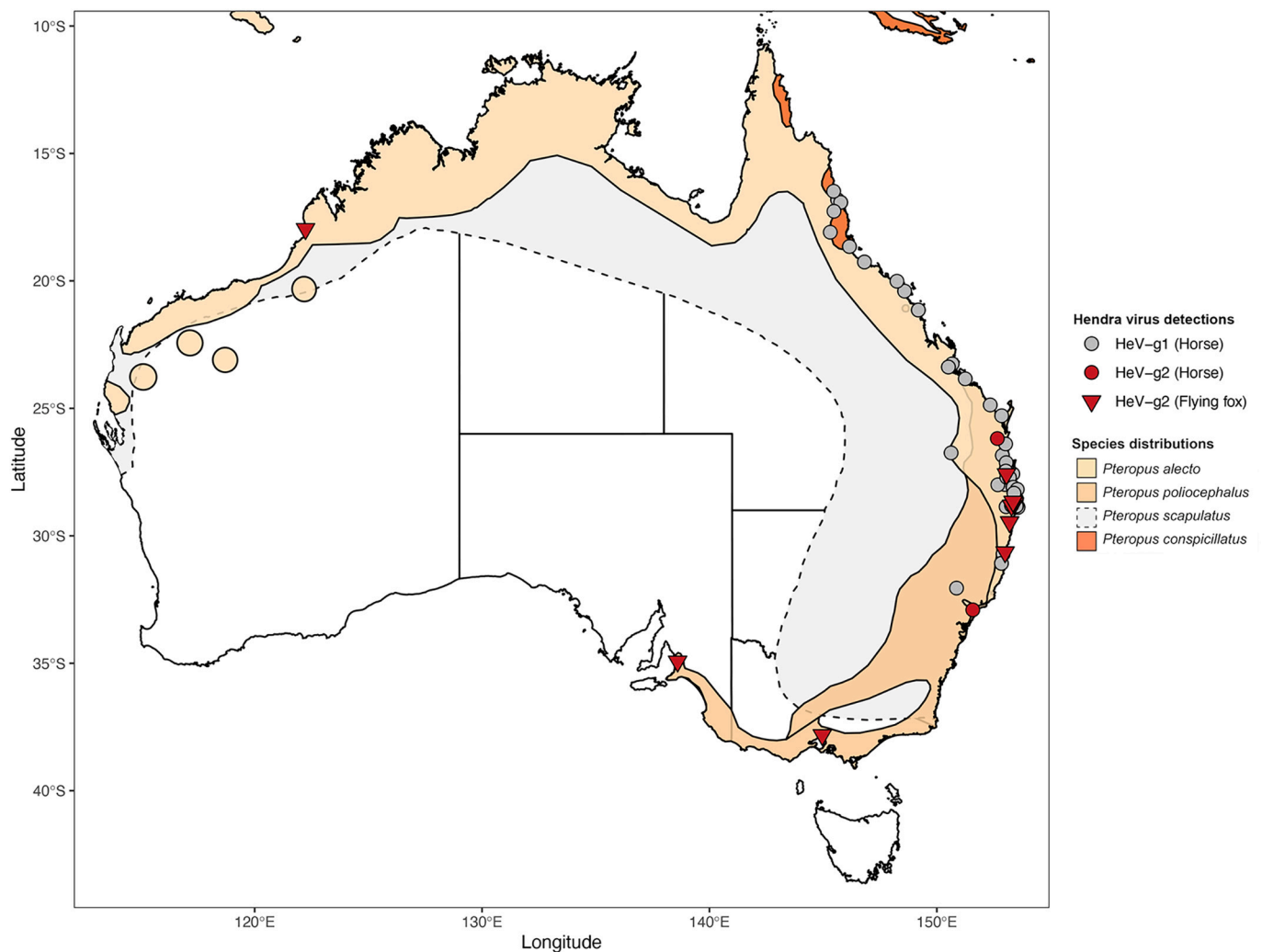


Fig. 2. Locations of equine Hendra virus genotype 1 (HeV-g1) and genotype 2 (HeV-g2) spillover events detected between 1994 and 2021 (including Newcastle City case) and detections of HeV-g2 in flying foxes since 2013. Location data was obtained from recent publications and Queensland Government: ‘Summary of Hendra virus incidents in horses’. [3,24,25] Shading denotes distribution of *Pteropus* spp. flying-foxes by species (*Pteropus alecto* cream, *Pteropus poliocephalus* tan, *Pteropus scapulatus* grey with dotted outline, and *Pteropus conspicillatus* orange).

horse’s airway and respiratory expiration. Eleven contacts with potential exposure were interviewed by HNEPHU officers on their health daily for 21 days following their exposure. No symptoms consistent with HeV infection were reported, and no contacts underwent testing for HeV infection.

Compared with previous HeV case investigations, responsive active surveillance sampling, and thorough investigation of flying-fox activity by bat ecologists was limited due to COVID-19 pandemic movement restrictions [21]. It was not possible to determine with certainty whether flying-foxes were actively foraging on the property in the lead up to, and following, this HeV-g2 spill-over event. Nevertheless, a team of wildlife rehabilitators investigated flying-fox activities the week following the event, observing nearby roosts and potential foraging areas near the property. The aggregated count from four roosts within 20 km of the property totalled approximately 10,000 flying-foxes, which was within the historically recorded range for this region during spring [27]. The two roosts nearest the property were not occupied at the time of the event or during the putative time window of spillover transmission. Occupied roosts were located 12 km and 18 km from the site, with aggregated estimates of grey-headed flying-foxes and black flying-foxes of approximately 6000 and 4000 respectively. The species were unevenly distributed, and only grey-headed flying-foxes were observed at the occupied roost nearest the event. Flying-foxes were heard within

trees in the paddock and seen flying overhead by the owners during their time farwelling the diseased horse in the evening of the 5th of October.

Media releases and public communications, aiming to address public concern and encourage awareness and risk mitigation (including vaccination) for horses in the region, were led by New South Wales Department of Primary Industry representatives beginning 7 October. The national Equine Veterinary Association prompted veterinarians attending horses to be proactive in considering HeV infection in light of the event.

No additional HeV-g2 cases were detected and biosecurity directions ended on 27 October.

4. Outcomes and lessons learned

Detection of this high consequence novel zoonotic infection of a horse in the greater Newcastle region, Australia, is testament to rapid implementation of a new diagnostic test by animal health laboratories, in June 2021, following the research discovery of the HeV-g2 sub-lineage. Fortunately, no additional domestic animal or human disease cases occurred during or after the periods of animal quarantine and post-exposure monitoring of human and animal contacts.

Interestingly, while detections of HeV-g1 spillover infection of horses has predominantly been in the southern winter, this HeV-g2 spill-over

occurred in the middle of spring (Fig. 3). As of June 2022, of 65 recognised HeV spill-over events detected since 1994 in Australia, this event is only the fifth to occur during October. 69% of events (45) have occurred during June, July or August [3]. This seasonal trend in detected HeV spill-over, coincides with peak winter seasonality in detection of HeV in flying-fox excreta, with hypothesised influences including seasonal reproductive activity, physiological stress, and effects of anthropogenic activity (land clearing) on winter native feeding sources [8,9,28,29]. There is currently insufficient data to infer differences in seasonality of HeV-g1 and HeV-g2 excretion from flying foxes.

Nevertheless, these perspectives highlight the benefit of proactive surveillance of wildlife through research integrated with government biosecurity initiatives for emerging viruses, including application of both open-ended and targeted molecular testing of urine collected via under roost sampling over space and time to inform spill-over risks beyond those currently widely appreciated [24,25].

This is the first contemporary diagnosis of HeV-g2 infection in a horse, and is the southernmost detection of HeV in a horse in Australia, consolidating recent recognition that the geographical risk of bat-to-horse spill-over infection is greatly expanded from that previously understood and communicated [22–25]. Investigators noted typical clinical features of HeV infection, including rapid clinical deterioration featuring marked mucous membrane changes and encephalitic manifestations, yet relatively mild respiratory manifestations and without recognised pyrexia. The 2015 Queensland horse case, retrospectively determined to have been infected with HeV-g2, presented similarly with acute disease onset, rapid deterioration over 24 h, congested mucous membranes, tachycardia, tachypnoea, normal rectal temperature, muscle fasciculations, head pressing, and collapse [22]. It is important to emphasise that clinically observed manifestations of HeV infected horses may vary widely depending on the time window and opportunity for examination relative to the course of infection and disease. Thus veterinarian consideration of HeV as a differential diagnosis may be best-informed by understanding the pathologic basis of disease in the context of the expected range of manifestations observable during disease progression [12].

The described case features consolidate prior evidence supporting that HeV-g1 and HeV-g2 are of equivalent pathogenicity. This suggests that unidentified historical infections of horses with HeV-g2, resulting in horse fatalities and unmanaged risk of human illness, are likely to have occurred. As such, there is a need to proactively test horses that die suddenly or present with consistent disease manifestations in all regions of Australia that host flying-foxes [12,22].

The described case highlights previous concerns identified in HeV investigations in the Hunter Valley involving horses kept in peri-urban locations for companion and leisure purposes [21]. Specifically, it reinforces the need to tailor risk communication strategies (including

promotion of horse immunisation) for the full range of horse owners/carers, not only those affiliated with an industry network or subject to industry standards and policies [30]. The 2019 Hunter Valley case attracted considerable local and national media attention, which may have contributed to the reported 75% increase in individual horses, receiving at least one vaccine dose within a 40 km radius of the property in the 90 days following the event compared with the 90 days prior (Zoetis, per communication).

Finally, horse owners and close human contacts of the described case reportedly experienced profound stress in response to notification of confirmed HeV-g2 infection, intensive case investigations, and resulting media attention. Factors exacerbating this stress included personal health concerns relating to close exposures among those who came to farewell the horse, and their grief experienced following the sudden loss of a horse that had been much loved. Further research is required to understand owner behaviour and perspectives following death of horses of high relative sentimental value due to high consequence zoonotic diseases (such as HeV), especially to guide veterinary communications and biosecurity case management.

5. Conclusion

This contemporary HeV-g2 detection in a horse in the greater Newcastle region, Australia, supports understanding of risk of HeV spill-over from bats to horses as extending beyond the familiar geographical area outlined by prior HeV-g1 cases and concerns of potential past and future missed case detections [5,22]. Horse owners in any region where flying-foxes are likely to be present (regardless of species) should be proactively informed of implementable precautions to prevent bat-to-horse HeV spill-over infection - most-reliably vaccination [31].

This Newcastle HeV-g2 spill-over event also highlights ongoing need for vigilance among horse carers and veterinarians outside of the winter season. Given HeV vaccine for humans is currently lacking, prevention of human infection relies on horse vaccination and disease prevention initiatives across the full spectrum of human-horse interactions in rural and peri-urban settings where flying-foxes may be present.

The presented case accentuates the need for psycho-social research to better understand, anticipate, and address human responses to horse deaths. Such insight may inform development of more effective strategies for increasing compliance with biosecurity advice essential for protecting both human and animal health.

Integrated and collaborative approaches engaging veterinarians, animal, wildlife, and public health research and government agencies, as exemplified by this case, fundamentally support strategic proactive emerging disease surveillance and effective timely interagency responses fundamental to One Health and biosecurity. The Food and Agriculture Organization of the United Nations (FAO), the World

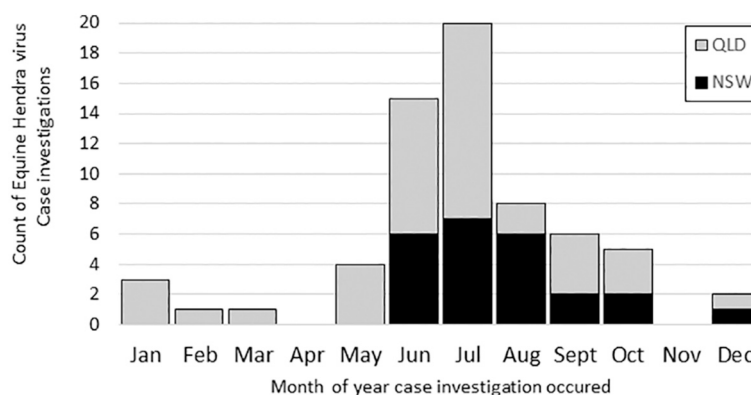


Fig. 3. Equine Hendra virus spillover infection events recognised between 1994 and 2021 (including Newcastle City case) by month of death. Each count represents one spillover event, in which one or more horses may have been affected. Queensland cases are shown in grey while New South Wales cases are shown in black. Derived from Queensland Government: 'Summary of Hendra virus incidents in horses'. [3]

Organization for Animal Health (WOAH formerly OIE), the United Nations Environment Programme (UNEP), and the World Health Organization (WHO) recently recognised that One Health is “an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems” [32]. The successful implementation of a One Health approach is characterised by effective collaborations and relationships between broad sectors, disciplines, and communities and the biosecurity governance framework that supports them. In the context of HeV in Australia, this requires operative collaboration, knowledge and expertise of: horse owners and wildlife rehabilitators; government officials (spanning public health, animal health, and environmental health); and a broad range of research disciplines, including biological, ecological, medical, veterinary, environmental and social sciences. Together, One Health partnerships can effectively reconcile the risk for the broad range of horses and their carers across all regions of potential risk of HeV spill-over events.

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Contributorship

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Joanne Taylor: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Kirrilly Thompson:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision. **Edward J. Annand:** Investigation, Writing – review & editing, Visualization. **Peter D. Massey:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision. **Jane Bennett:** Methodology, Investigation, Writing – review & editing. **John Sebastian Eden:** Investigation, Writing – review & editing, Visualization. **Bethany A. Horsburgh:** Investigation, Writing – review & editing, Visualization. **Evelyn Hodgson:** Methodology, Investigation, Writing – review & editing. **Kelly Wood:** Methodology, Investigation, Writing – review & editing. **James Kerr:** Methodology, Investigation, Writing – review & editing. **Peter Kirkland:** Investigation, Writing – review & editing, Visualization. **Deborah Finlaison:** Investigation, Writing – review & editing, Visualization. **Alison J. Peel:** Methodology, Investigation, Writing – review & editing, Visualization. **Peggy Eby:** Methodology, Investigation, Writing – review & editing. **David N. Durrheim:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

Authors do not have a commercial or other association that might pose a conflict of interest. De-identified data on vaccination rates were supplied by Zoetis Inc.

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