Hendra virus (HeV)

Pathogen

Hendra virus (HeV)

Overview

The HeV blood phase has not been well defined as infection is extremely rare with only seven infections reported in humans ever. It is not known to be transfusion-transmissible. Although it is classified as a catastrophic severity agent with a high mortality rate, it is a low risk to blood safety because infection is exceedingly rare.

Classification and morphology

HeV is named after the Brisbane suburb of Hendra where the virus was first isolated in 1994. Retrospective testing of stored samples from a number of species including rodents, marsupials, birds, amphibians and insects found no evidence of HeV prior to 1994. Therefore the first recorded outbreaks of HeV in 1994 appear to have signalled the emergence of a novel virus.

HeV is classified within the *Paramyxoviridae* family, *Orthoparamyxovirinae* subfamily and *Henipavirus* genus. HeV was originally classified as a member of the *Morbillivirus* genus and referred to as equine morbillivirus. The HeV genome is a non-segmented single-stranded RNA molecule. Within the *Paramyxoviridae* family, the HeV genome is unusually large at approximately 18,000 nucleotides.

HeV is closely related to Nipah virus (NiV), another species within the *Henipavirus* genus. NiV was first identified in Malaysia in the late 1990s but has not been reported in Australia. The two viruses share antigenic similarities and amino acid sequence homology that varies between 71% and 92% across the different regions of the genome. In 2012 the isolation and characterization of a new paramyxovirus from pteropid bats in Cedar Grove in South East Queensland was reported. The virus, referred to as Cedar virus (CedPV), shares significant features with the known henipaviruses and has now been classified as a species within the *Henipavirus* genus.

[1–6]

Associated disease

Although there is some variation in the clinical symptoms of HeV infection, which may reflect differences in viral strains, respiratory and/or neurological symptoms are the primary manifestations in both horses and humans. In the original outbreak in 1994, acute respiratory disease with high fever was reported in infected horses while influenza-like symptoms were reported in humans (including fever, cough, sore throat, headache and tiredness). During the 2008 outbreak, the main symptoms reported in infected horses and humans were neurological. Neurological symptoms in horses include uncoordinated gait and muscle twitching rapidly leading to death. In humans, HeV infection is associated with encephalitis, the symptoms of which include headache, high fever and drowsiness, progressing to convulsions, coma and death.

The incubation period of HeV in horses appears to range between 3 and 16 days. Up to 70% of infected horses die, usually within 36 hours of infection. The time from exposure of a person to an infected horse and the onset of clinical symptoms is between 5 and 21 days. Since 1994 there have been four human deaths from HeV infection from a total of seven confirmed human

infections. The second fatal case of HeV infection in a human was a 35-year-old male who developed meningitis from which he made a full recovery. However, 13 months later he became ill and died of encephalitis 25 days after admission to hospital.

[1-3,7-13]

Blood phase

Due to the small number of confirmed human HeV infections, the blood phase of HeV infection has not been well defined. However, if similar to the closely-related and more common NiV, a brief and low-level viraemia would be expected in acute human HeV infection. Based on the three surviving cases of HeV and studies of NiV cases, IgM appears within two weeks post-infection and remains detectable for several months in recovered patients. IgG seroconversion occurs from three weeks post-infection and may remain detectable for years. In the three cases that survived HeV infection, virus was shed for 5−6 weeks post-exposure with no evidence of shedding after this time.

[13-15]

Chronic carriage

Although data are limited due to the small number of human HeV cases, the possibility of chronic carriage of HeV in humans is indicated by a reported case of relapsing HeV-associated encephalitis some 13 months after recovery from primary infection.

[7-9]

Human exposure routes

The primary mode of human exposure to HeV is thought to be from exposure to respiratory secretions and/or blood of infected horses. Horses are the only species known to be naturally infected from flying foxes, and HeV has been isolated from the equine nasopharyngeal secretions, saliva, urine, foetal material and organs. To date, all reported human HeV cases have had exposure to equine respiratory and/or oral secretions, body fluids and/or blood from infected horses. However, only a relatively small proportion of people associated with infected horses show serological evidence of exposure to HeV, indicating that the virus is not efficiently transmitted to humans from horses.

Human-to-human and bat-to-human transmission of HeV has not been reported. However, human-to-human and bat-to-human transmission of the closely relate NiV has been reported, the latter associated with drinking date palm juice contaminated with fruit bat saliva, urine and faeces. As date palm juice is not usually consumed in Australia, this may explain the absence of reported bat-to-human HeV transmission to date.

[1,6,8,15,16]

Vector and reservoir

The natural host of HeV is the fruit bat genus *Pteropus* (known as flying foxes). Evidence of HeV infection has been detected in all four species of fruit bat found on the mainland of Australia (*P. alecto. P. poliocephalus, P. conspicillatus and P. scapulatus*) with seroprevalence rates varying between 20% and 50%. Additionally, HeV has been isolated from all of these species except *P. scapulatus. P. alecto* and *P. conspicillatus* are

thought to represent the primary sources of spill over infection to horses based on more frequent HeV isolation in these two species. It is likely that HeV has co-evolved with the fruit bats as the virus does not cause disease in the bats and retrospective testing of bat samples from the 1980s indicated an anti-HeV prevalence rate similar to current rates.

Given the high seroprevalence of HeV in fruit bats and the temporal clustering of bats in areas where there have been outbreaks of HeV in horses, viral spill over from bats to horses is the most plausible explanation of equine infections, although horse-to-horse transmission may infrequently occur. All known outbreaks of HeV in horses have occurred in tropical or sub-tropical regions of Australia where fruit bats are common and there is a strong association between the location of equine cases and the density of fruit bats. The precise mode of transmission from bats to horses has not been defined but exposure to urine, faeces, saliva or birthing products from infected fruit bats are considered possible mechanisms. HeV does not appear to transmit efficiently from bats-to-horses, horses-to-horses or horses-to-humans.

The proximate cause of HeV spill over has not been clearly defined. However, features common to equine outbreaks include thoroughbred breeds, age <8 years, housing in a paddock, season and presence of flying fox food or roost trees in the paddock. It has been proposed that spill over to horses may not be sporadic but reflect an episodic pattern of infection in fruit bats whereby an outbreak of HeV infection in a colony of fruit bats reaches a threshold proportion of infected bats, resulting in a peak of virus excretion and increasing the probability of equine infections in the vicinity. This is indicated by winter peak excretion in flying foxes paralleling a winter peak of equine cases.

[1, 2, 6, 17-22]

At risk populations

The people most at risk of HeV infection include horse owners and trainers, veterinary personnel, horse dentists, farriers and any persons in close contact with horses in areas susceptible to equine HeV outbreaks. All reported cases of equine HeV infections have been in Queensland or northern NSW and all reported human cases have been in Queensland.

[6, 23]

Transfusion-transmissibility

Due to the relatively small number of human HeV infections (seven), the transfusion-transmissibility of HeV has not been defined.

Treatment and efficacy

Ribavirin and chloroquine have been used to treat HeV-infected patients but with limited success. Prophylactic immunoglobulins are now available. There is no registered human vaccine for HeV.

In November 2012 a recombinant subunit HeV vaccine for horses was commercially released. Trials with the vaccine demonstrated that it protected horses from direct oronasal challenge with a lethal dose of HeV for up to six months. The vaccinated horses showed no clinical symptoms and did not shed any detectable virus.

[1, 13, 14, 23-25]

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Assay and algorithm options for screening and confirmatory / diagnostic testing

There are a number of testing methodologies available at reference laboratories for the detection of HeV including viral isolation, immunohistochemistry techniques and electron microscopy. HeV RNA can be detected by real time polymerase chain reaction (PCR) or conventional reverse transcriptase PCR (RT-PCR). There are several assay formats for the detection of anti-HeV including serum neutralisation test (SNT), enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA) and micro particle immunoassay (MIA).

The definitive criteria for HeV laboratory case definition is one of the following: (i) isolation of HeV from clinical material or (ii) detection of HeV RNA in clinical material by nucleic acid testing (NAT) or (iii) detection of seroconversion or four-fold or greater rise in Hendra virus-specific IgM or IgG titres. Anti-HeV detection should be confirmed by at least one alternative method and SNT is regarded as the gold standard.

[1, 2, 24, 26, 27]

Lifeblood risk assessment: blood components

HeV is an emerging infectious disease pathogen that represents a theoretical risk to blood safety in Australia but considered low risk given human cases are extraordinarily rare. Human HeV infection includes a viraemic phase which may precede symptoms indicating the potential risk of an asymptomatic viraemic donor presenting to donate.

Since HeV was first identified in 1994 it appears to have spread geographically and reported equine outbreaks have continued to be reported. Following the first identified outbreak in 1994 and one case reported in 1999, outbreaks in northern NSW and Queensland have become significantly more frequent since 2004. In 2011 the largest annual number of outbreaks was reported with 18 separate outbreak sites and 24 infected horses. To September 2018 there had been a total of 104 reported equine cases of which 84 (80.7%) were reported in Queensland and 20 (19.3%) in NSW. During the same period there were seven reported human cases with four fatalities, all reported in Queensland between 1994 and 2008.

There is potential for HeV to spread to other mammals as indicated by the two reports of naturally infected dogs (2011 and 2013) and, in addition, guinea pigs and cats have been experimentally infected. Fruit bat habitats are expanding as indicated by a study which found that *P. alecto* has moved about 1,000 km south down the eastern coast of Australia since the 1930s, reaching Sydney in 2007; the study also found that *P. alecto* can travel a total distance of 3,000km over a 342-day period. It is expected the range of the *Pteropus spp*. will continue to move south, possibly as a result of climate change. In addition, fruit bats infected with HeV were detected for the first time in South Australia in 2013.

The level of ongoing risk of human exposure to HeV will depend on the extent of uptake of the horse vaccine by horse owners which will, in part, depend on the efforts of governments and vets to promote the vaccine. Widespread uptake of the vaccine has the potential to substantially reduce the risk of human exposure.

Although the equine vaccine became available in late 2012, equine HeV cases have continued to be reported to September 2018, indicating a need for greater uptake of the vaccine.

In summary, at present HeV represents a low risk to blood safety in Australia given the small number of reported human cases, the last of which was reported in 2009.

[2, 14, 23, 25, 28–33]

Current Lifeblood risk management strategy for blood safety

Donor deferrals exist for allogeneic/therapeutic donors with current or recurrent infection, past infection and contacts with infectious disease. These deferrals are regularly reviewed and any outbreaks or new developments are constantly monitored.

Proposed strategy should local outbreak occur

In the event of a significant local outbreak of HeV, Lifeblood may perform a risk assessment to determine whether additional risk mitigation measures were required. Potential strategies include the implementation of a supplementary question to identify donors visiting/residing in risk.

Leucoreduction efficacy

No data is available.

Pathogen reduction efficacy (fresh components)

There is no licensed pathogen reduction technology (PRT) available in Australia, but this could be a future option assuming effective RBC technology is realised. Specific HeV inactivation data is not available for the commercial pathogen reduction technologies.

Pathogen reduction efficacy (plasma derivatives)

All of CSL Behring's (CSLB's) plasma-derived products include specific virus inactivation or virus removal steps designed to ensure viral safety.[35]

Further information available on the CSL Behring website:

https://www.cslbehring.com/products/safety-and-manufacturing

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