Ministry for Primary Industries
Manatū Ahu Matua

Hendra virus requirements for horses

With special consideration of horses vaccinated against Hendra virus and trans-Tasman trade

Technical advice document prepared for Animal Imports and Exports by Risk Analysis.

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Executive Summary

Hendra virus in horses has been found in the Australian states of Queensland and New South Wales. It is an organism exotic to New Zealand that may cause very serious disease in horses and humans, including death. It is a disease primarily of horses but in some outbreaks, albeit rarely, humans have been infected.

Since the discovery of the virus in 1994, seven humans have been infected and four died as a result. Regarding Australian horses, so far 76 have died or been euthanased because of infection with Hendra virus. There is no specific treatment available for infected humans or horses.

A two year trial of a Hendra virus (HeV) vaccine for horses commenced in Australia on the 1st November 2012. Vaccinating horses that reside in regions where infected flying foxes reside may be an effective strategy to prevent virus shedding from infected horses, thus interrupting transmission of HeV to humans. Hence, an effective vaccine would prevent disease in horses and also humans.

The disease is not listed by the World Organisation for Animal Health (OIE). Therefore, there are no international trade recommendations to minimise the likelihood of HeV being introduced when importing horses. Moreover, there are no vaccines recommended by the OIE or serological tests that allow differentiation of vaccinates from naturally exposed horses. Also, there are no OIE recommended antigen tests for international trade.

This document examines the risks associated with importing vaccinated horses and documents the rationale for Import Health Standard (IHS) requirements. Current measures require the disease to be notifiable in Australia, and horses be clinically healthy when exported, and from premises free of HeV for the past 3 months. Therefore, measures do not require vaccination or diagnostic testing.

It is concluded that the use of the trial vaccine in Australian horses does not significantly change the risk of introducing HeV when importing horses. Moreover, horses inoculated with the approved vaccine do not pose any biosecurity risk.

Hypothetically, when the efficacy of the vaccine has been demonstrated in the field, and once the booster vaccination timing is known, vaccination could be considered as a possible requirement for trade purposes.

However, at this time, the current measures effectively manage the risk and there is no advantage in requiring horses to be vaccinated or to introduce testing.

Nevertheless, the current IHS requirement of 3 months premises freedom could be considered unduly trade restrictive. The incubation period of HeV infection in horses is up to 16 days and typically 8-11 days. In Australia, all disease incidents are managed by a 30 day quarantine period for affected premises and testing of all in-contact animals. Quarantine is lifted 30 days after the last positive test result.

Therefore, an IHS requirement that horses are kept on premises that are free from quarantine restrictions can be considered all that is necessary.

Accordingly, it is recommended that changes be made to the IHS in this regard.

Introduction

On the 14th November 2012, the Australian Chief Veterinary Officer notified MPI of the release of a Hendra virus vaccine for use in horses in Australia. The vaccine is supplied and administered under strict conditions set by the Australian Pesticides and Veterinary Medicines Authority. The *Equivac HeV* vaccine is commercially produced by Pfizer for horses and is available only from veterinarians who have been specifically accredited.

MPI Animal Imports and Exports requested technical advice from Risk Analysis on possible risks associated with importing HeV vaccinated horses. Documentation of the rationale for current import requirements was also requested.

Additionally, this technical advice may be shared with the International Movement of Horses Committee (IMHC). This Industry group aims to facilitate the international movement of racehorses. Government organisations are not members of the IMHC, but may participate as observers.

Nonetheless, the primary purpose of this document is to provide support to MPI Animal Imports when determining import policy decisions with respect to HeV, particularly importing horses that may have been vaccinated and are thus seropositive.

Aetiological agent

Family *Paramyxoviridae*, genus *Henipavirus*, species Hendra virus.

Hendra virus (HeV) is indigenous to all four species of flying fox (*Pteropid* spp. of fruit eating bats) found in Australia.

New Zealand's status

Hendra virus is listed as an unwanted and notifiable organism.

Epidemiology

Outbreaks of HeV infection in horses occur infrequently in Queensland and New South Wales. The reservoir host, Australian flying foxes, infect horses as a spillover event whereby horses may then transmit infection to humans who are in close contact with them.

Fruit bats carry the virus with no noticeable disease. A combination of ecological and horse husbandry factors appears to contribute to the risk of spillover events. The specific manner of transmission from flying foxes to horses remains uncertain, but the virus is readily recoverable from urine under trees in which flying foxes are roosting or feeding. Experimental studies have shown that horses are infected by the oral route (Marsh et al 2011).

There have been 39 outbreaks reported involving 76 horses since the virus was first identified in 1994. Most of these horses died or were euthanased. HeV infection is a disease primarily of horses but in some outbreaks human infections have occurred, albeit rarely. Seven people have been infected with the virus and four have died (APVMA 2012; Mahalingam et al 2012).

Transmission to humans has almost always occurred through physical contact with nasal and oral secretions emanating from very ill, dying or dead horses. Epidemiological findings have suggested that one person may have been exposed to an infected horse incubating the disease (Marsh et al 2011; Snary et al 2012). Nevertheless, all cases in humans have been acquired from close contact with infected horses. Experimental data on viral quantities confirm that the febrile and sick horse likely pose the greatest transmission risk, whereby post-mortem examination of horses poses the greatest risk to humans becoming infected (Marsh et al 2011).

Human infection is characterised by an acute encephalitic syndrome. The case fatality rate is high (Mahalingam et al 2012). Therefore, the development of the vaccine for use in horses presents an important opportunity to help prevent disease in horses, but also to protect humans from a fatal disease for which there is no effective treatment.

The incubation period in horses ranges from 4-16 days, but is typically 8-11 days. Clinical signs of HeV infection in horses may be subclinical or mild through to severe. For instance, clinical signs may include depression, ataxia, tachycardia, fever and rapid death for acutely affected horses with severe respiratory distress (Snary et al 2012; Marsh et al 2011). Horses displaying clinical signs may survive infection. Both field and experimental studies have shown that although horizontal transmission may occur, this is unusual since horses are not highly infectious (Snary et al 2012).

It is not known conclusively whether horses are capable of being chronically infected or not. In a horse that developed clinical signs of infection and recovered, virus could be recovered from its spleen 8 days after clinical signs had ceased. This indicates that horses may recover from infection but still harbour the virus (Williamson 2004).

Further, the relationship between the onset of clinical signs and duration of viral shedding has not been determined. In two of three horses experimentally infected HeV RNA was detected continuously in nasal swabs from as early as 2 days post-infection. These results suggest that nasal secretions of subclinically infected horses may pose a risk during the early phase of disease that precedes viraemia, fever, or other noticeable clinical signs. However, the investigators note that the transmission risk posed is relatively low when compared with animals that are clinically affected. Viral RNA was detected in tissues sampled at post-mortem examination up to 9 days post-infection, when the experiment concluded (Marsh et al 2011).

HeV is not considered to be highly contagious. Experimentally infected horses did not transmit infection to horses or cats that were kept in-contact (Williamson et al 1998). This is consistent with observations in field outbreaks where disease does not become wide-spread and can be contained to affected premises. Therefore, HeV is characterised by its poor transmissibility (World Organisation for Animal Health 2012; Field 2012; Williamson 2004; Williamson et al 1998). Experimentally, a cat infected by injecting large amounts of the virus subsequently transmitted infection to a horse. However, cats are not important in the epidemiology of the disease and there are no reports of natural infection in cats.

Dogs, like cats, seem to be resistant to natural infection although there is a solitary report of a seropositive dog, probably from exposure to three infected horses on the same property (Field 2012). Therefore, dogs may very rarely be infected when exposed to heavily contaminated environments. However, the dog was not clinically affected. It is not known whether dogs are able to transmit infection or become chronic carriers. However, since the dog was only subclinically infected, it is likely that they are dead-end hosts.

Experimental studies have demonstrated that a subunit vaccine based on a soluble version of the HeV attachment glycoprotein G successfully prevent productive HeV infections in ferrets and in horses (Pallister et al 2011; APVMA 2012).

Therefore, vaccinating horses that reside in regions where infected flying foxes are present may be an effective strategy to prevent virus shedding from infected horses, with the resulting interruption of transmission of HeV to humans. Thus an effective vaccine would prevent disease in horses and also humans. This is because all cases in humans have been acquired from close contact with infected horses and there have been no reports of people being infected directly from flying foxes or through human-to-human transmission (Pallister et al 2011).

OIE international trade recommendations

The OIE aims to provide transparency in the global animal disease and zoonosis situation and safeguards world trade by publishing health standards for international trade in the *Terrestrial Animal Health Code*.

Harmonisation ensures a consistent approach to addressing risks and means that countries should base their SPS measures on relevant international standards where they exist.

However, in regards of HeV, the disease is not listed by the OIE and there are, therefore, no international trade recommendations to minimise the likelihood of HeV being introduced when importing horses.

New Zealand's Hendra virus measures

The SPS Agreement requires that any restrictions on trade that are needed to achieve a country's level of protection be non-discriminatory, transparent and scientifically justified. HeV has been identified in New Zealand's Import Risk Analysis: Horses and horse semen (2000) as a hazard in the importation of horses.

The justification for imposing measures to manage the potential consequences of importing HeV infected horses is documented in the risk analysis (Stone 2000). For convenience, the risk management Section from the risk analysis has been appended.

Were HeV to be introduced, an eradication response would be initiated. It is highly likely to be successful since horses are not highly infectious and human-to-human transmission has not been reported. It is highly unlikely that the infection would become widespread and the virus could not establish here since fruit bats, the reservoir host, are not present in this country.

Nevertheless, quarantining infected horse properties, and tracing horses and people that may have been exposed to infection would require a significant disease incursion response engaging animal and public health authorities. This would involve short-term direct consequences for the affected persons and properties. The virus would have direct consequences on the health and welfare of horses. Humans in close contact with an infected horse could be at risk of infection.

For international trade, some countries require Australian horses to be tested for evidence of HeV infection prior to shipment. Should HeV be reported in New Zealand, those same

countries could demand testing of our horses prior to export. However, this would probably be a short-term effect, with re-negotiation of conditions once it had been demonstrated that the disease did not establish here. This notwithstanding, it is difficult to predict how trading partners would react and there could be suspension of trade or additional testing measures imposed on horses prior to export. Depending on the strictness of measures imposed, associated costs would affect the horse industry and could potentially be trade disruptive and expensive.

In conclusion, introduction of HeV could have significant health impacts on individual horses and humans who might be exposed to them and unfortunate enough to be infected.

Therefore, New Zealand's measures to prevent the introduction of HeV continue to be justified.

OIE diagnostic tests

The OIE prescribes no HeV-related measures for international trade in horses. Nevertheless, the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (hereafter referred to as the *Manual*) does provide laboratory standards for identifying HeV and describes serological and antigen tests for diagnosis. Diagnosis of disease caused by HeV can be by virus isolation or detection of viral RNA in clinical or post-mortem tissue samples (World Organisation for Animal Health 2012).

For serological diagnosis, identification of antibodies is less useful because of the high case fatality rate of infection (death before detectable antibody response).

Nevertheless, detecting specific antibody to HeV in horses is of diagnostic significance since horses may recover from infection and because of the rarity of infection and serious zoonotic potential. There are two serological tests described in the *Manual*; the virus neutralisation test and the ELISA (World Organisation for Animal Health 2012).

Although there are several serological and antigen tests described in the *Manual* none are recognised as prescribed tests for the purpose of international trade.

The APVMA approved vaccine

Eqivac HeV, a commercially manufactured HeV vaccine has recently been released in Australia. An Australian Pesticides and Veterinary Medicines Authority (APVMA) Permit, which expires August 2014, has been issued to Pfizer Animal Health.

In clinical trials involving a small number of horses, the vaccine has shown complete protection when vaccinated horses were subject to lethal challenge with a virulent strain of HeV. All vaccinated horses were protected from disease and neither HeV nor evidence of virus replication was detected in any tissue of the immunised horses. The vaccine induced antibodies prevented infection by binding to the G protein of the virus, rendering it unavailable for attachment to the cells of the horse.

Veterinarians must undergo a special accreditation process before being permitted to administer the vaccine. The conditions outlined in the APVMA Permit require horses' details (which include microchip identification and location) and vaccine details (date given, batch number etc) to be meticulously recorded in a National Online Registry maintained by Pfizer

Animal Health. The information recorded in the Registry must be available at all times to the Australian Chief Veterinary Officers. This is because there is no serological test to differentiate between antibodies induced by vaccination and those caused as a result of natural exposure to the virus. Therefore, in the event of a disease outbreak, horses that have been vaccinated can be differentiated from those naturally exposed to the virus by consulting the Online Registry.

Therefore, at this early stage of release, vaccination is available on a constrained basis. While the vaccine may prevent clinical disease, the APVMA warns that it should not be assumed that vaccinated horses cannot contract the disease. For vaccination to be effective it must take place before exposure, and immunity must be maintained by repeated vaccination. Each horse will require an initial vaccine followed by a booster 21 days later. The extent and duration of effect of booster doses have not been studied (APVMA 2012). However, research is underway on how frequently booster doses will be required to maintain immunity. It is likely that protection will require an ongoing vaccination programme, the details of which are yet to be determined.

With the information available at this time, vaccination can be considered adjunctive, or as an aid in the prevention of clinical disease caused by HeV. For trans-Tasman trade, vaccination is not considered to offer equivalence to existing import requirements. Therefore, it should not be relied upon to replace the principal risk mitigation measures of HeV being a notifiable disease, premises freedom, and horses to be clinically healthy at export to prevent HeV introduction.

Over time, current measures may be modified to include a vaccination option once booster vaccination requirements that provide on-going immunity are known. Needless to say, although the vaccines clinical trial shows immense promise, the vaccine must prove effective in protecting against natural challenge. Once the efficacy of the vaccine is demonstrated in the field, it may be possible to consider vaccination as an option for trade purposes. For instance, an alternative to the current measures could be based on vaccination, with the horse showing no clinical signs of HeV on the day of shipment and having been vaccinated not less than 21 days and no more than 12 months prior to shipment (these times are currently arbitrary, given the absence of specific information on the length of immunity induced).

The biosecurity risk from importing vaccinated horses

The majority of horses imported are from Australia, New Zealand's largest trading partner. The Australian Veterinary Association recommends that all horses should be vaccinated against HeV. In particular, horses in the known higher risk areas (AVA 2012).

Initially horses residing in Queensland and New South Wales are likely to be vaccinated since the vaccine has been prioritised for those high risk parts of Australia. However, over time it is probable that most imported horses will be seropositive as a result of vaccination.

The APVMA approved vaccine (*Equivac HeV*) does not contain genetically modified organisms and there is no live or inactivated virus in the product. The vaccine contains Hendra virus G glycoprotein as the only active constituent (APVMA 2012).

For these reasons, there is no biosecurity risk posed from importing vaccinated horses from Australia.

Recommendation

Hendra virus outbreaks continue to occur relatively rarely and sporadically in parts of Australia. At this time it is not possible to evaluate the effectiveness of the vaccine being trialled and the impacts it may have on clinical disease in horses and humans in the future.

However, the evidence presented warrants continuation of measures against HeV in horses, despite the recently released vaccine. Measures in New Zealand's IHS are scientifically justifiable since horses from Australia are considered to pose an ongoing risk of introducing HeV.

Therefore, it is recommended that measures for HeV should be maintained in the IHS for horses from Australia. However, requiring 3 months premises freedom could be considered unduly trade restrictive. The incubation period in horses is up to 16 days and typically 8-11 days. In Australia, all disease incidents are managed by a 30 day quarantine period for affected premises and testing of all in-contact animals. Quarantine is lifted 30 days after the last positive test result (Schipp 2012).

Recommended measures:

1. Infection of horses with HeV is a notifiable disease in Australia; *and*

2. ~~During the 3 months~~ prior to export the horses were kept on premises free from quarantine restrictions for HeV ~~where infection of horses with HeV had not occurred during that period~~; *and*

3. The horses were showing no clinical signs of infection with HeV on the day of export.

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Appendix- Risk management section from IRA 2000

15.10 Risk management

15.10.1 Risk management objective

Horses clinically infected or incubating HeV and Nipah virus should not be imported. Horses should be protected from infection in the pre-export period.

The short incubation period and obvious and acute clinical signs associated with HeV infection in most horses make clinical freedom the most important safeguard.

The serological response to HeV has not been well defined, although limited data suggest that by the time a detectable titre of antibody is produced the horse will probably have manifest acute respiratory disease. Persistence of infection and the possibility of the carrier state require further investigation. The benefit of serological testing in the absence of clinical signs would probably only be to ensure that recovered or subclinically infected horses were not imported.

HeV titres and tissue distribution during the acute phase of clinical disease were much greater than those recorded in a horse that had recovered from clinical disease. Virus was not recovered from horses that had been subclinically infected. Transmission from horses with acute disease to other animals could not be demonstrated.[14] This suggests that the likelihood of subclinically infected or recovered horses transmitting infection is probably negligible, and that safeguards aimed at preventing any such event (i.e serological testing) are unwarranted.

Similar investigations into Nipah virus have not yet been undertaken in horses. Considering the greater distribution and incidence of infection in Malaysia, serological testing of horses for Nipah virus is probably warranted. Either the IgG or IgM capture ELISA or SNT should be considered acceptable.

Protection from infection in the pre-export period could be achieved by measures to restrict the area or premises from which imports are permitted, or by requiring horses to undergo a period of pre-export isolation. The outbreak areas appear to be confined to particular states in the affected countries, although the environmental factors that contribute to outbreaks have not been well-defined. The presence of a reservoir host, suggested to be fruit bats, may be a contributing factor. Excluding access by fruit bats to horses being prepared for export could reduce the risk of infection in the pre-export period.

Outbreaks of disease in horses are rare and acute events that receive widespread publicity, international attention, and investigation by animal and public health authorities in Australia and Malaysia. Infection with HeV is notifiable in all states and territories of Australia (pers. comm. Tim Buick, AQIS, 22 June 1999). The control and eradication programme for Nipah virus during the 1998-1999 outbreak has involved mass culling of infected pigs and widespread surveillance in many species. [5]

So long as HeV and Nipah virus remain notifiable and there is a swift response to disease outbreaks, a premises of origin disease freedom statement covering the 3 month period prior to

export provides the most practical option to achieve protection from infection in the pre-export period.

15.10.2 Risk management measures

Live horses

Either:

1. The horses were resident since birth, or at least the previous 3 months, in a country that is free of HeV and Nipah virus.

Or:

1. The horses were imported from Australia, where infection of horses with HeV is a notifiable disease; *and*

2. During the 3 months prior to export the horses were kept on premises where infection of horses with HeV has not occurred during that period; *and*

3. The horses were showing no clinical signs of infection with HeV on the day of export.

Or:

1. The horses were imported from Malaysia, where infection of horses with Nipah virus is a notifiable disease; *and*

2. During the 3 months prior to export the horses were kept on premises where infection of horses with Nipah virus has not occurred during that period; *and*

3. During the 30 days prior to export the horses were tested for Nipah virus using either the IgG or IgM capture ELISA or SNT, with negative results; *and*

4. The horses were showing no clinical signs of infection with Nipah virus on the day of export.