Submission No. 28

From: [redacted]
To: Agriculture and Environment Committee
Subject: Hendra information for review
Date: Monday, 29 February 2016 11:39:59 AM
Attachments: Hendra letter.docx
Geoffrey Playford - Hendra Doc.pdf

To whom it may concern

Thank you so much for investigating this issue.

Like many other horse owners, I'm now in a situation where all local vets are refusing to treat unvaccinated horses, even for cases that do not involve bodily fluids. Note: ALL human Hendra infections have occurred as a result of **extensive unprotected exposure to bodily fluids via invasive procedures.** No human has caught Hendra from incidental contact.

I have a pony that has had toxic laminitis issues, so her health is under my watch. Unfortunately, she is not well at the moment and I have no access to veterinary treatment. Obviously, vaccination is not an option for her. This leaves me in a situation where if needed, I will arrange for a neighbour to shoot my pony if she is suffering. It's a sad situation, as so many owners like myself have planned for their horses demise.

I believe part of the issue with proof of vaccine injury death is in the **HOW this 'proof' is assessed**. It is extremely difficult to obtain a definitive proof of vaccine damage. APVMA don't even appear to have that as an option. The highest level is that of 'probable'. The problem is that the majority of owners don't even know they can report adverse events, and those that do mention it to their vet are often told it's not due to the vaccine. Then there are other owners that assume the vaccine is safe and don't put 'two and two' together.

I've attached a letter (and a pdf referenced document) I recently drafted as an education tool for vets. It has a lot of of information and links that I researched. I hope it might be of assistance for you.

The challenge is in getting vets to wear PPE, which is something doctor's, nurses and paramedics accept as a normal part of their daily work. In the medical world, doctors already dealt with this issue way back in the mid 1800's. Yes, roughly 165 years ago there was a doctor (Ignaz Phillip Semmelweis) who made the connection between women's deaths in childbirth and germs on obstetrician's hands. Of course, it was some time before his theory was accepted and hand washing/disinfecting practices were introduced. This was because doctors couldn't accept that they could be responsible for spreading infections. Fast forward to the aids epidemic in the late 1980's. The Aids Council out of necessity, introduced the condom wearing campaign "If it's not on, it's not on." This helped reduce Aids infections.

Sadly here we are today, trying to educate a number of vets to do the right thing and 'put it on'.

Feel free to contact me if you have any questions.

Regards

Marion Carrick
Stanthorpe QLD 4380

Dear (Name)

I have found you to be a wonderful vet. I'm truly grateful for your sensible and practical assistance over the years. In turn, I was concerned and saddened on receipt of your letter outlining the clinic's new Hendra policy.

Don't worry; this is not going to be a nasty letter. Rather, I thought I had a responsibility to let you know the result of my extensive research on Hendra and its potential risks. I did this as I had wanted to ensure the safety of my horse/s, and anyone (such as yourself) interacting with them.

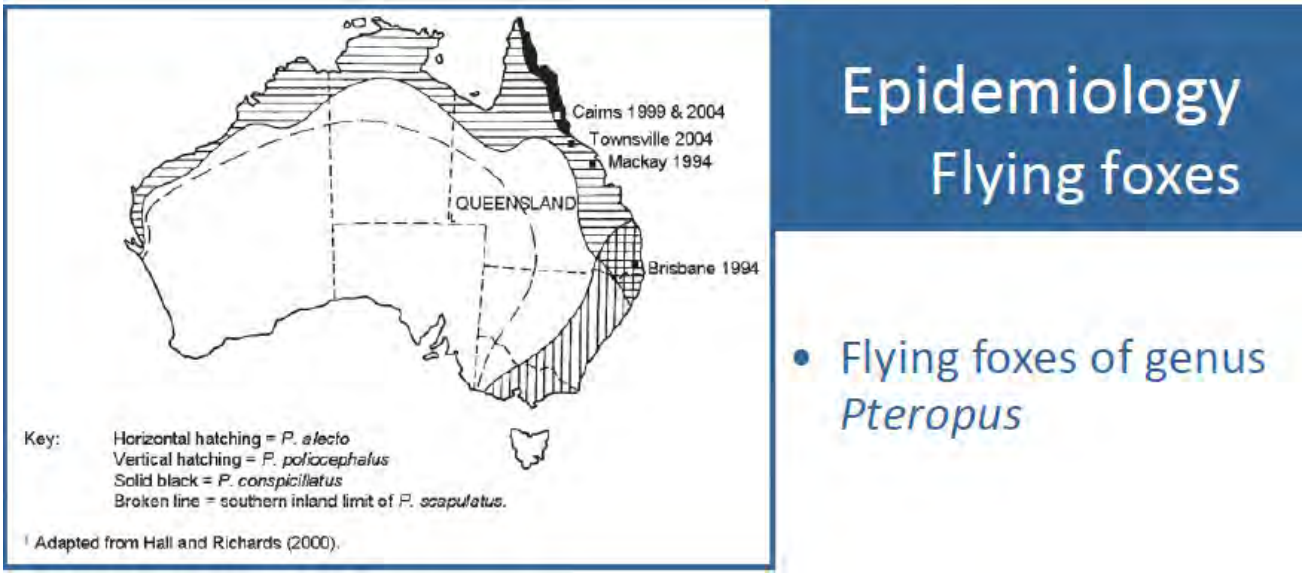
I know the letter is quite long. However, I couldn't include the important information and references, had I shortened it. I'd really appreciate it if you could please take the time to read this information, and let me know your thoughts.

Hendra Virus

It is believed Hendra is transmitted to horses via exposure to flying fox bodily fluids. This mostly occurs during cooler months.

"The route of natural infection of horses by HeV is <u>not known</u>, but it is likely that primary exposure occurs via the upper respiratory tract and/or the oropharynx." Qld DAF

The suspected Hendra carrying flying fox species are found in Queensland. However, some of these species are also found in every Australian state and territory (excluding Tasmania). There has been no Hendra case within (time) hours' drive of (town).



<u>Hendra is unstable</u> - *"Hendra virus is very fragile. It is easily killed by heat, soap or detergents and by desiccation (drying out). It may survive in the environment from several hours to several days depending on environmental conditions. Survival is longer in cool moist conditions where the pH is close to neutral." - Nsw DPI*

<u>Hendra is rare</u> - *"Despite the recent cluster of cases in 2011, the spillover of Hendra virus to horses is a rare event."* Qld DAF

Of the **horses** infected with Hendra virus:

- 100% died – Current government policy is the euthanasia of ALL Hendra infected horses and other animals. It is expected 25% would have survived. (Qld Ombudsman)
- It is likely that a number of horses infected at the Hendra, Redlands, and Cawarral incidents caught the virus due to contaminated fomites (including human-assisted transfer), rather than from a 'natural infection'

pathway. (Qld Ombudsman) As a result, the true number of Hendra cases should have been considerably lower.

Of the **people** infected with Hendra virus:

- **None** wore PPE
- Approximately 50% died
- Only 10 – 20% of people with ***unprotected, significant exposure*** caught Hendra (Qld Health)
- **ALL** were performing invasive procedures – eg. necropsy, or nasal lavage (Qld Health)

Hendra is hard to catch - *"Hendra virus is not highly contagious and it requires close contact with infected animals (including their body fluids and tissues) for infection to be transmitted to other animals or humans."* Qld DAF

Transmission studies found… *"Transmission from P poliocephalus to horses could not be proven and neither could transmission from horses to horses or horses to cats. Under the experimental conditions of the study the virus is not highly contagious." (*Pubmed)

Hendra virus is simply very difficult to catch.

www.daf.qld.gov.au/animal-industries/animal-health-and-diseases/a-z-list/hendra-virus/general-information

www.daf.qld.gov.au/animal-industries/animal-health-and-diseases/a-z-list/hendra-virus/research/initial-research

www.daf.qld.gov.au/__data/assets/pdf_file/0015/65220/HeV-Initial-experimental-characterisation.pdf
www.dpi.nsw.gov.au/agriculture/livestock/horses/health/general/hendra-virus/faqs

www.ncbi.nlm.nih.gov/pubmed/9972433

www.ombudsman.qld.gov.au/Portals/0/docs/Publications/Inv_reports/Hendra/Hendra_Virus_Report_web_V1.pdf

Hendra Vaccine

If horse owners knew the vaccine was 100% safe and 100% effective, I believe the vast majority of owners would vaccinate, irrespective of the cost. Unfortunately, the Hendra vaccine is most certainly NOT safe, and its effectiveness is yet to be proven.

Despite concerns from horse owners, the Hendra Virus vaccine (Equivac HeV) was registered on 4 August 2015. It is described on the APVMA label as:

*"An aid in the prevention of **clinical symptoms** of the disease caused by Hendra virus in horses 4 months of age and older."*

The Hendra Virus vaccine label also states:

- The vaccine is "adjuvanted with immunostimulating complex."
    - The adjuvant of the Hendra vaccine has drawn a lot of public criticism and concern. It is worth noting the lack of detailed adjuvant information on the vaccine label. However, Violin states the Hendra adjuvant is called "CpG DNA Vaccine Adjuvant", and that it has "the strongest immunostimulatory effects on mouse immune cells in vitro", and is still **under clinical trial**!

- "The potential for vaccinated horses to shed virus if exposed to and infected with the Hendra virus cannot be ruled out."

    - It is concerning that a *vaccinated* horse could be asymptomatic and still be shedding the virus.
    - I believe it is riskier treating an asymptomatic vaccinated horse.
    - Owners are more likely to be complacent with a vaccinated horse.

- "The product should not be used in sick or immunocompromised horses."

    - There are potentially a number of horses in this region that meet this criterion.

- "The effect on pregnant mares, or horses intended for breeding is not known."

    - Some equestrian studs are having (post HeV vaccination) conception and live foal guarantee issues with *non-maiden* mares.
    - Permit 14876 states Zoetis is not liable for *"The failure of any horse to conceive or maintain a pregnancy following use of The Product."*

- "The effectiveness of Equivac HeV in the face of Hendra virus disease outbreak has not been studied."

    - Government departments do not require vaccines to be proven effective (antibody-antigen affinity) before being released onto the market. Only that they are capable of producing a certain number of antibodies (titers), which is defined as "vaccine efficacy."
    - Being able to produce measurable antibodies, does not make a vaccine effective in the protection against disease.

- "The compatibility of Equivac HeV Hendra virus vaccine with other vaccines and veterinary chemical drugs has not been studied."

- Personal Protective Equipment (PPE) should be worn whenever Hendra virus disease is suspected even in vaccinated horses as not all vaccines can provide a guaranteed protection."

<u>Adverse Reactions & Vaccine Safety</u>

- A condition of the HeV vaccine permit *"Registered veterinary surgeons must report to Zoetis any adverse reactions, including lack of efficacy, resulting from the use of The Product within 48 hours of observing or being notified of an adverse reaction."*

    - Some vets were in breach of the previous permit conditions by not reporting adverse reactions and advising owners that the health issues were not due to the vaccine.
    - Only APVMA can make a decision about whether, or not an adverse experience is associated with the HeV vaccine.

- There are APVMA recorded (probable), as well as a significant number of anecdotal cases of Hendra vaccine injury, or death. Unfortunately, it is reasonable to believe there are many more.

- Owners are still often unaware of the appropriate reporting pathways to APVMA
- There is some ignorance to the fact that vaccines can cause damage/death. Because of this ignorance, many owners have not made the correlation between the vaccine and the injury/death.
- As a result, I believe the true statistical results of Hendra vaccine harm are likely to be markedly higher than currently published.

www.violinet.org/vaxjo/vaxjo_detail.php?c_vaxjo_id=10

http://websvr.infopest.com.au/LabelRouter?LabelType=L&ProductCode=68996

Professional Code of Conduct

"The Australian Veterinary Association Code of Professional Conduct presents and promotes a body of ethical principles to guide veterinarians' conduct in their relationships with patients, clients, colleagues and the community. Whilst this Code reflects the professional commitment of AVA members, it should be relevant to all practicing veterinarians."

The AVA Code of Conduct is an 8 point, multi-faceted policy. Below are two of the relevant points:

Always consider the health, welfare and respectful treatment of the animal

a) Veterinarians should recommend appropriate preventive measures and provide suitable management and treatment for disease conditions. Although actions may be influenced by consideration of a client's commercial, financial, emotional or other circumstances, *veterinarians should not condone animal suffering, nor be party to it.*

Strive to provide the best possible veterinary services, and to improve the quality of animal health and welfare.

a) Veterinarians have a responsibility to provide the best veterinary services within the prevailing circumstances, and should strive to improve the quality of those services.

By refusing treatment of an unvaccinated horse, surely that's a breach of the veterinary ethical principles?

http://www.vsb.qld.gov.au/avacode.html

Workplace Health & Safety

There has been a lot of recent speculation around Hendra virus and supposed requirements of Queensland's Workplace Health & Safety (WPH&S) on veterinary clinics.

WPH&S recommend:

- Hendra vaccination – but not mandatory
- The use of PPE for all horses, vaccinated or not

WPH&S have ***no requirement*** for vets to only treat Hendra vaccinated horses.

www.worksafe.qld.gov.au/__data/assets/pdf_file/0010/82981/alert-hendra-infoforvet.pdf
www.worksafe.qld.gov.au/__data/assets/pdf_file/0010/83098/outcome-audit-hendra-vet-industry.pdf

Human Risks

- No person has caught Hendra from normal, incidental contact.

- *"Not surprisingly, the activity that is likely to pose the **highest** transmission risk is post mortem examination, on account of the virus load present in the animal at the time, the opportunity for gross contamination of operator and assistants with infective material, and the inherent risks associated with the handling of sharps."* Qld DAF

Below are a number of tables taken from a Queensland Heath Department document. They relate to risk of infection, use of PPE and treatment leading to infection with Hendra virus – see attached 'Geoffrey Playford – Hendra Doc' document.

Human clinical manifestations

Case	Date	Exposure to infected horses	Clinical syndrome	Outcome
1: 40-yo stable hand	Sept 1994	Respiratory secretions	'Influenza-like' illness	Recovery, no relapse
2: 49-yo horse trainer	Sept 1994	Respiratory secretions	Pneumonitis, multi-organ failure, fatal	Died (day 13 illness)
3: 36-yo farmer	Aug 1994	Assisted with necropsy	Initial aseptic meningitis with recovery (Aug 1994) Relapsed with encephalitis 13 months later (Sept 1995)	Died (day 25 illness)

Human clinical manifestations

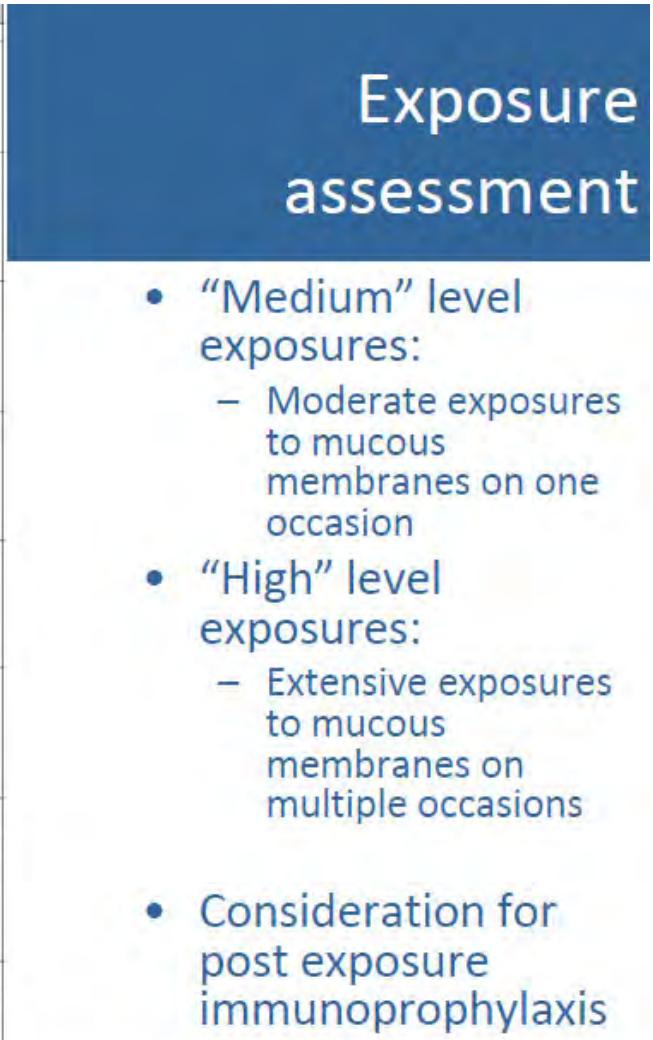
Case	Date	Exposure to infected horses	Clinical syndrome	Outcome
4: Veterinarian	Nov 2004	Performed necropsy	'Influenza-like' illness	Recovery, no relapse
5: 33-yo Veterinarian	July 2008	Respiratory secretions, performed necropsy	Acute encephalitis	Died (day 31 illness)
6: 21-yo Veterinary nurse	July 2008	Respiratory secretions	Acute encephalitis	Recovery, persisting neurological deficits
7: 51-yo Veterinarian	August 2009	Respiratory secretions	Acute encephalitis	Died (day 19 illness)

Summary table: Humans with high risk exposure to equine HeV – numbers and percentage infected

Public Health investigations
Follow-up of humans exposed to equine HeV

Outbreak	Number exposed	PPE use	Infection
Hendra, 1994	8 close contact with infected horses	0%	2 (25%)
Thornlands, 2008	14 staff with "high risk" exposures	7%	2 (14%)
Cawarral, 2009	4 stud workers with "high risk" exposures	0%	1 (25%)

6. EXPOSURE ASSESSMENT table		
Nature and magnitude of exposures	**Assessment**	**Management**
No exposure to dermis and/or mucous membranes	Nil	Reassurance Information Serology Other testing Referred to GP Other
Slight to extensive exposures to intact dermis on <3 occasions	Negligible	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Adequate and consistent use of appropriate hand hygiene with intact skin and only skin contact	Negligible	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Adequate and consistent use of PPE without breaches	Negligible	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Slight to extensive exposures to intact dermis on 3 or more occasions	Low	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Slight exposures to mucous membranes or uncovered wounds on 1 occasion	Low	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Moderate exposures to mucous membranes or uncovered wounds on 1 occasion	Medium	Initial assessment Final assessment after discussion with IDP Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Extensive exposures to mucous membranes and/or uncovered wounds and/or needlestick injury on single or multiple occasions without adequate PPE e.g. kissing horse on muzzle, being drenched with oral or respiratory secretions, undertook respiratory tract procedures such as endoscopy or nasal lavage, performed or assisted with post mortem	High	Initial assessment Final assessment after discussion with IDP Referred Contact to IDP Reassurance Information Serology Other testing Referred to GP Restriction, donation Other



The above table demonstrates the use of PPE brings the potential risk of infection of Hendra virus - negligible to **Nil**.

Summary

- Hendra is a fragile virus that's both rare and difficult to catch.
- ***No*** government department, veterinary board, or association is recommending mandatory vaccination for treatment. This includes the following:
    - Queensland Health
    - Biosecurity Queensland
    - Australian Veterinary Association
    - Various insurance companies offering - veterinary professional indemnity insurance
    - Veterinary Surgeons Board
- Queensland Health Department documents state that people wearing PPE have a ***negligible to NIL*** risk of catching Hendra Virus.
- ***No*** person wearing PPE has caught Hendra
- The Hendra vaccine is ***not*** 100% safe, and ***not*** 100% effective.
- Horses are dying and suffering in pain… due to veterinary refusal of treatment, or significantly delayed treatment.

- More horses are likely to die from treatment refusal/delay than from Hendra virus.
- Even vaccinated horses need an exclusion test
- Colic and snake bite can fatal and potentially present with symptoms similar to Hendra. In this case, horses do not have time to wait for an exclusion test before treatment.

(Name), I understand your concerns with Hendra virus. However, as you can see I have researched extensively and I STILL don't understand why vets are refusing to treat horses. We all just need to wear PPE, particularly when undertaking invasive procedures. Is there other information that I'm not aware of?

I'll finish with an email for endurance riders regarding 'Hendra virus hysteria' from another vet, Dr Matthew Walker.

"As a vet, I have been curious about the hysteria around Hendra. So far vets, their spouses, or there staff have been the only people infected with Hendra since Vic Rail and his stable hand. I have a vested interest in this disease. No member of the public has got sick from patting, grooming, feeding or riding Hendra horses.

The pertinent question is risk. There are two types of risk - perceived risk and real risk. The perceived risk is dominating the current debate. The real risk is minute.

In the last 20 years 4 people have died from Hendra and 3 have survived. During the same period horses in Australia have killed 400 people and hospitalized 60,000. Horses themselves are a far greater risk than Hendra. Just ask your life insurance company - I did. Horse sports rate up there with Scuba diving, Bull riding, and sky diving as risk.

So we are willing to put our foot in a stirrup at midnight and canter through the bush - but are afraid of a disease that only infects people doing post mortems or nasal lavages.

600 people a year catch Dengue - 75% in Qld
The same number each year Leptospirosis - 60% in Qld
Hundreds get Q fever.
There are lots a bugs out there.

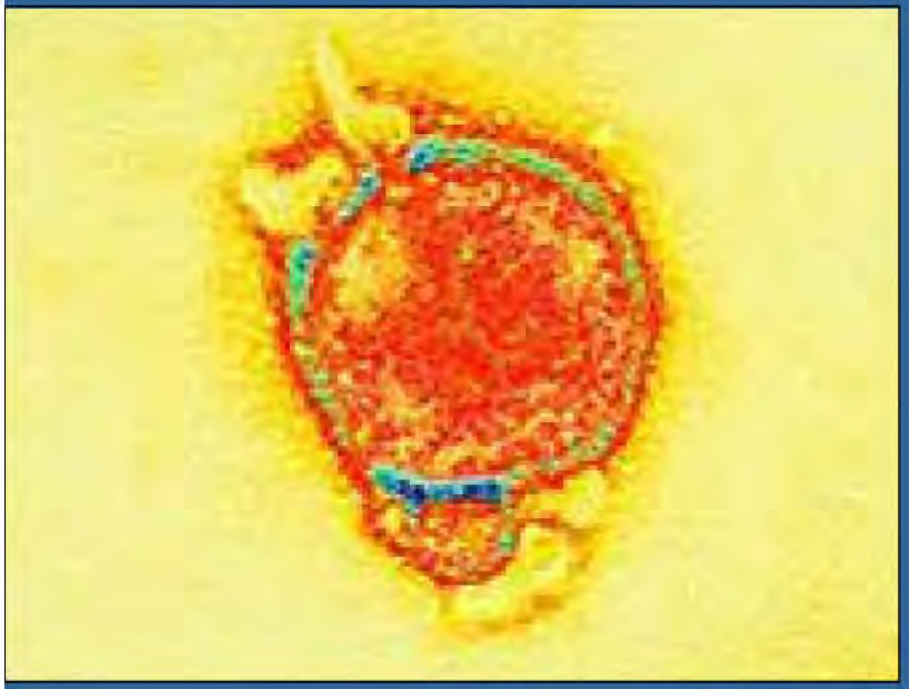
17,000 people die each year from medical negligence.

Some perspective on risk is needed…."

Thank you for taking the time to read this letter. I look forward to hearing your thoughts.

Regards

Hendra virus infection
A threat to horses and humans



Geoffrey Playford

Infection Management Services |
Princess Alexandra Hospital

Department of Microbiology |
Pathology Queensland

[redacted]

CaSS | Pathology Queensland
A CLINICAL AND STATEWIDE SERVICE

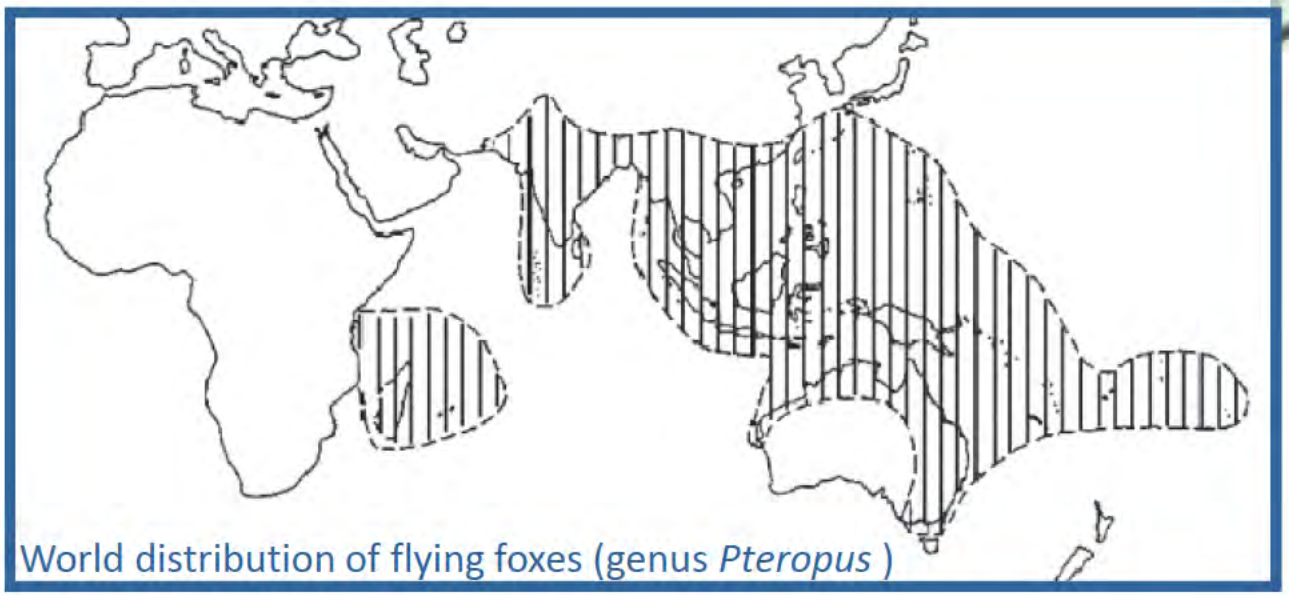
Overview

- Virology, pathogenesis
- Epidemiology
- Clinical disease in humans
- Histopathological, neuro-histopathological insights
- Prevention of human infection, public health responses
- Recent developments in therapeutics

Recently described paramyxoviruses associated with bats

- Hendra virus (Australia, 1994)
- Menangle virus (Australia, 1997)
- Nipah virus (Malaysia, 1998)
- Tioman virus (Malaysia, 1999)

Pteropus poliocephalus

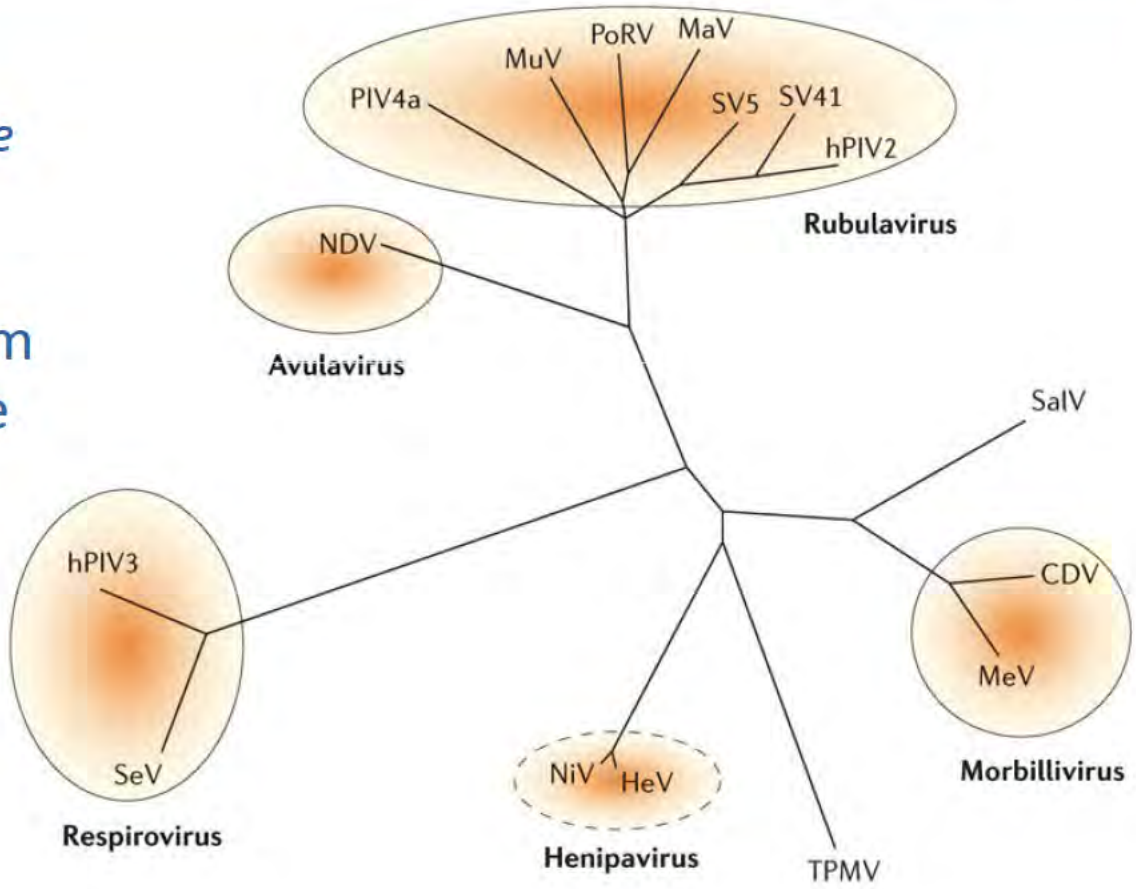


World distribution of flying foxes (genus *Pteropus*)

From: Field et al., CTMI 2007;315:133-59

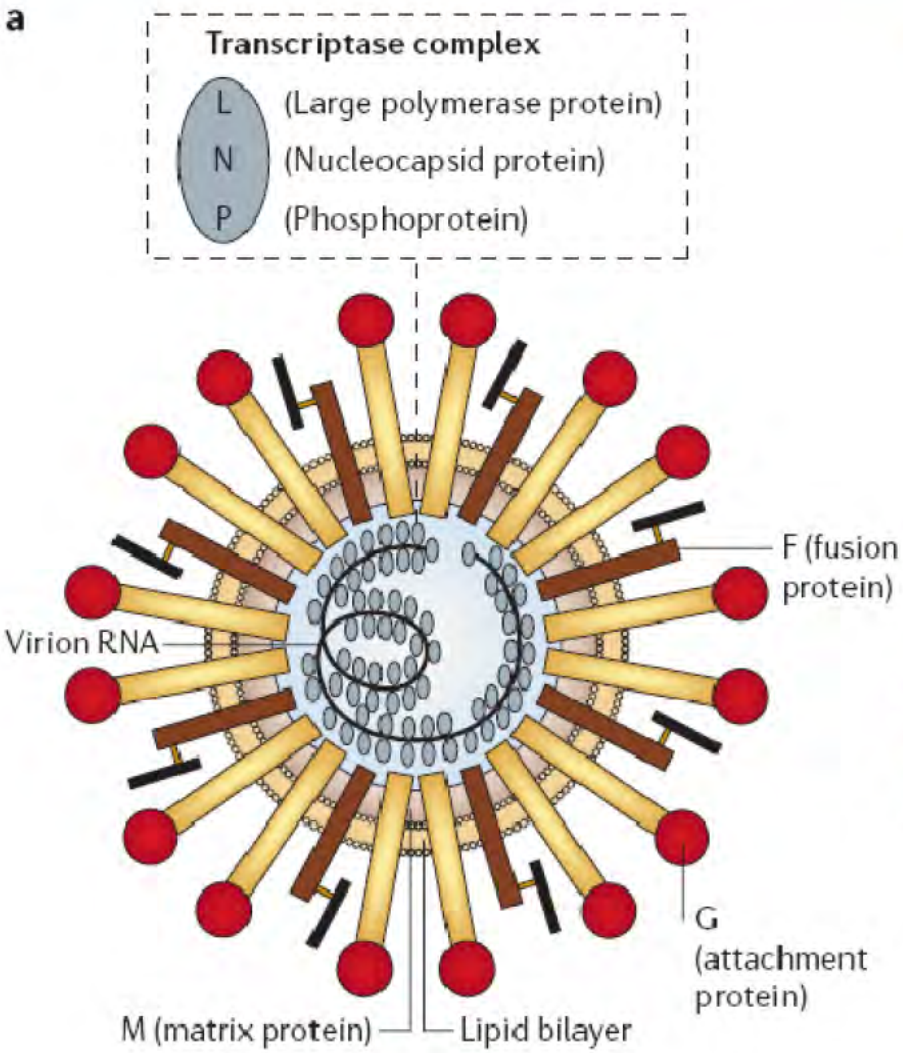
Background
Hendra virus

- Family *Paramyxoviridae*
  - Subfamily *Paramyxovirinae*
    - Genus *Henipavirus*
- First recognised 1994 from outbreak at Hendra horse stables in Brisbane
- Initially designated:
  - Acute equine respiratory syndrome
  - Equine morbillivirus

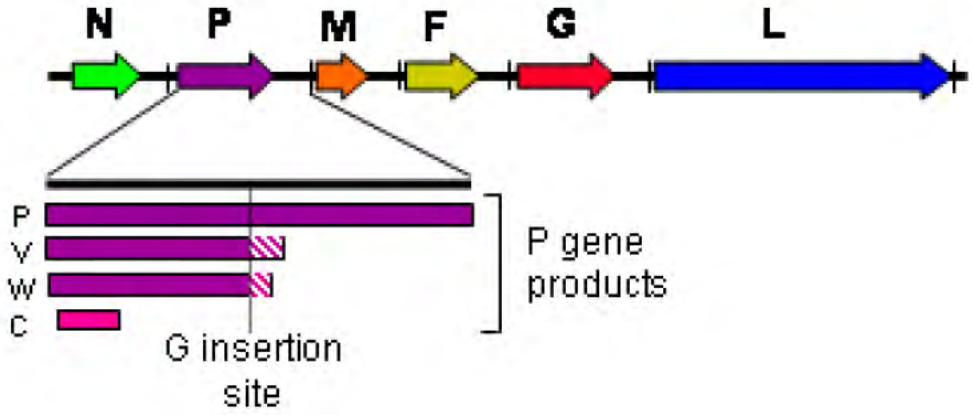


From: Eaton et al., Nature Rev Microbiol 2006;4:23-35

Hendra virus structure and genome

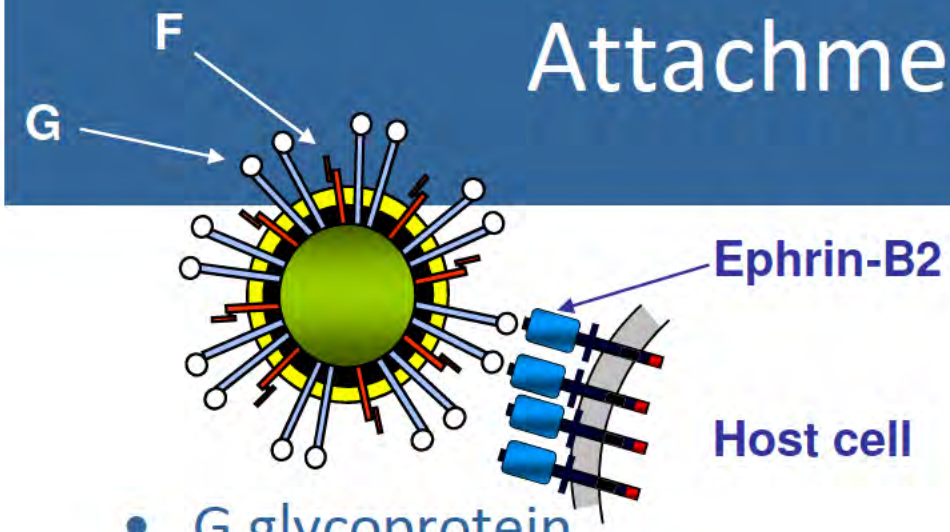


- Large genome: 18,234 nucleotides (~15% longer than most other paramyxoviruses)
- Typical paramyxovirus genome structure



From: Eaton *et al.*, Nature Rev Microbiol 2006;4:23-35

Attachment, fusion, cell entry

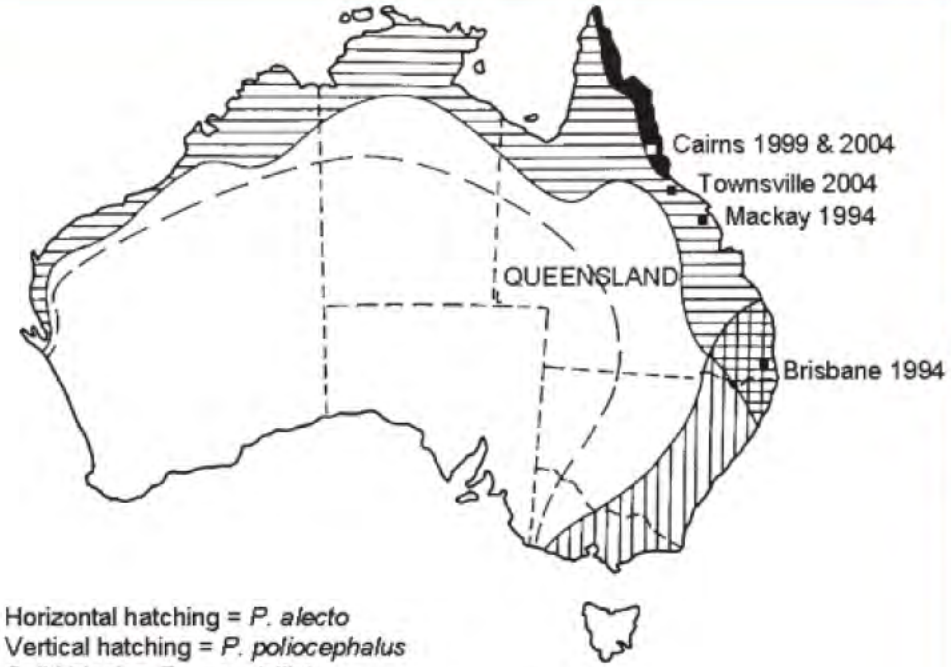


- Explains:
  - Broad host range
  - Systemic nature of infection

- G glycoprotein
  - Binds to **Ephrin-B2**
  - Highly conserved and ubiquitously-distributed surface glycoprotein
  - Present in small arterial endothelial cells & neurones
  - Ligand for **Eph** class of receptor tyrosine kinases
- F glycoprotein:
  - Precursor (F_0) cleaved into biologically active F_1 & F_2 by lysosomal cysteine protease **Cathepsin L** after endocytosis
  - Conformational change into **trimer-of-hairpins** structure

Bonaparte MI, *et al*. (2005). PNAS 102: 10652-57.
Negrete OA, *et al*. (2005) Nature 436: 401-405.
Negrete OA, *et al*. (2006) PLoS Pathog 2: e7.
Bishop KA, *et al*. (2007) J Virol 81: 5893-5901.
Bossart K *et al*. (2005). Virol J 2:57.
Pager CT *et al*. (2005). J Virol 79:12714-20.

Epidemiology
Flying foxes



[1] Adapted from Hall and Richards (2000).

- Flying foxes of genus *Pteropus*

- Seroprevalence ~50%
- HeV isolated from birthing fluids, placental material, and aborted pups
- Experimentally isolated from urine
- No apparent clinical disease
- Duration of infection, immunity & dynamics of infection within/between colonies uncertain
- Overlapping distribution of HeV & NiV between Australian & SE Asia

Field *et al*. CTMI 2007;315:133-59; Halpin *et al*. J Gen Virol 2000;81:1927-32

Epidemiology
Transmission

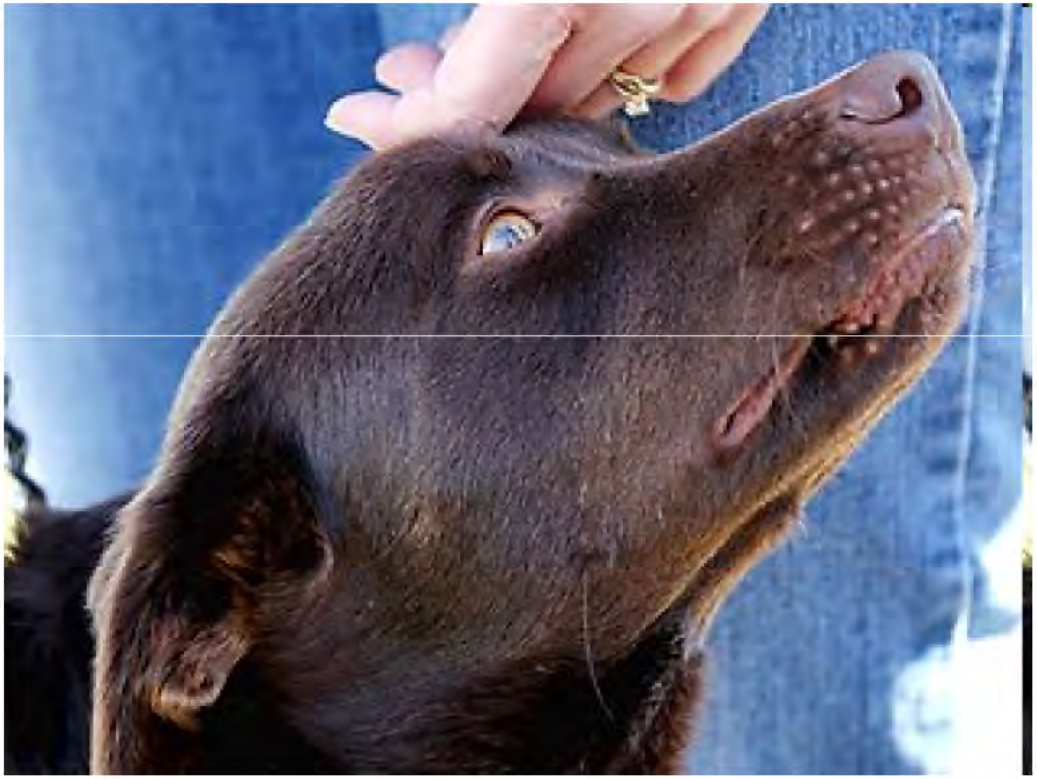
- Virions susceptible to desiccation[1]
- Bat-to-horse:
  - Contamination of pastures & feed with bat gestational products, urine, &/or spats
- Horse-to-horse:
  - More likely in stabled (rather than paddocked) situations
  - Contamination of stable environment/common equipment?

Observed epidemiology of NiV suggests bat-to-human & human-to-human *potential* of HeV

- Horse-to-human:
  - Droplet spread to mucosal surfaces with infected respiratory secretions
  - Direct contact to non-intact skin
  - Attack rate among highest risk exposures ~10-20%
- Bat-to-human:
  - Not documented in bat handlers despite extensive contact with saliva, urine, faeces etc
- Human-to-human :
  - Not documented in close domestic or HCW contacts

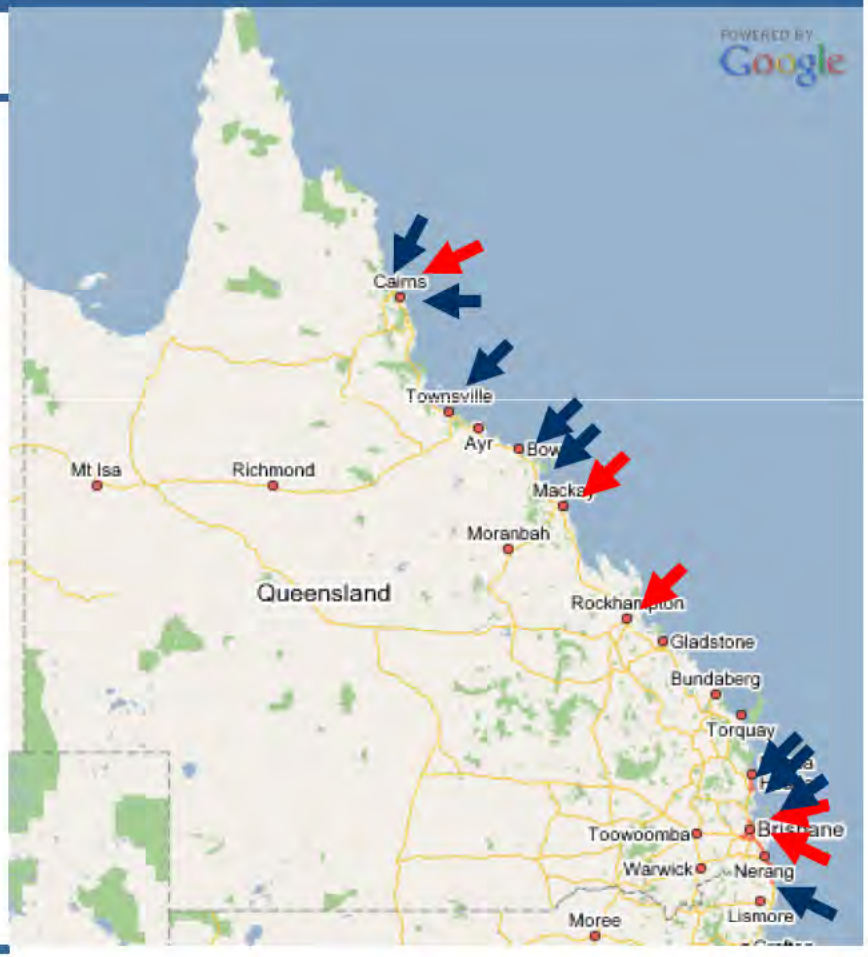
[1]Fogarty *et al*. Virus Res 2008;132:140-4

- Recent documentation of natural infection in dog:
  - ?from horse or bat
  - ?direct transmission from infected animal or indirectly from contaminated environment



HeV epidemiology
"Spill over" events: 1994-2010

Date	Location	Equine cases	Human cases
Aug 1994	Mackay, Qld	2	1
Sept 1994	Hendra, Qld	22	2
Jan 1999	Cairns, Qld	1	
Oct 2004	Cairns, Qld	1	1
Dec 2004	Townsville, Qld	1	
June 2005	Peachester, Qld	1	
Oct 2006	Murwillumbah, NSW	1	
June 2007	Peachester, Qld	1	
July 2007	Clifton Beach, Qld	1	
July 2008	Thornlands, Qld	5	2
July 2008	Proserpine, Qld	2	
Aug 2009	Cawarral, Qld	4	1
Sept 2009	Bowen, Qld	2	
May 2010	Tewantin, Qld	1	



- All events temporally associated with flying fox activity in region
- Equine index cases typically paddocked in areas attractive to flying foxes (fruiting trees etc)
- Apparent increase in "spill over" events

HeV epidemiology
"Spill over" events: 2011-

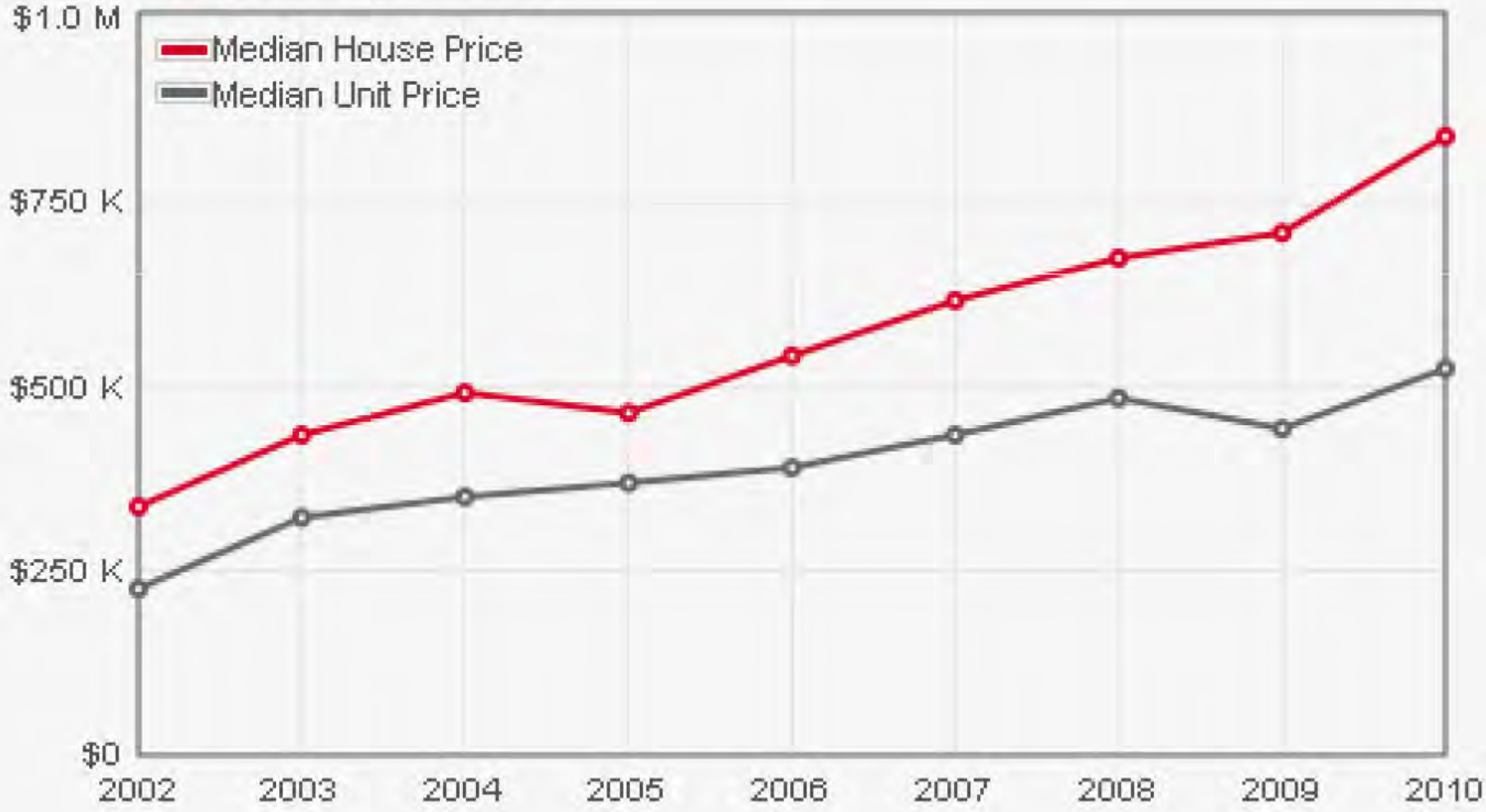
Date	Location	Equine cases	Human cases
June 2011	Beaudesert, Qld	1	0
July 2011	Wollongbar, NSW	2	0
July 2011	Boonah, Qld	3	0
July 2011	Park Ridge, Qld	1	0
July 2011	Macksville, NSW	1	0
July 2011	Lismore, NSW	1	0
July 2011	Kuranda, Qld	1	0
July 2011	Boondall, Qld	1	0
July 2011	Logan Reserve, Qld	1	0
July 2011	Hervey Bay, Qld	1	0
July 2011	Chincilla, Qld	1	0
July 2011	Mullimbimby, NSW	1	0
Aug 2011	Mullimbimby, NSW	1	0
Total		**61**	**7**

Hendra, Brisbane

Hendra, September 1994

- Explosive outbreak of unknown infectious agent involving 22 horses and 2 humans (1 fatal)

Median sale prices in Hendra



Human clinical manifestations

Case	Date	Exposure to infected horses	Clinical syndrome	Outcome
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3: 36-yo farmer	Aug 1994	Assisted with necropsy	Initial aseptic meningitis with recovery (Aug 1994) Relapsed with encephalitis 13 months later (Sept 1995)	Died (day 25 illness)

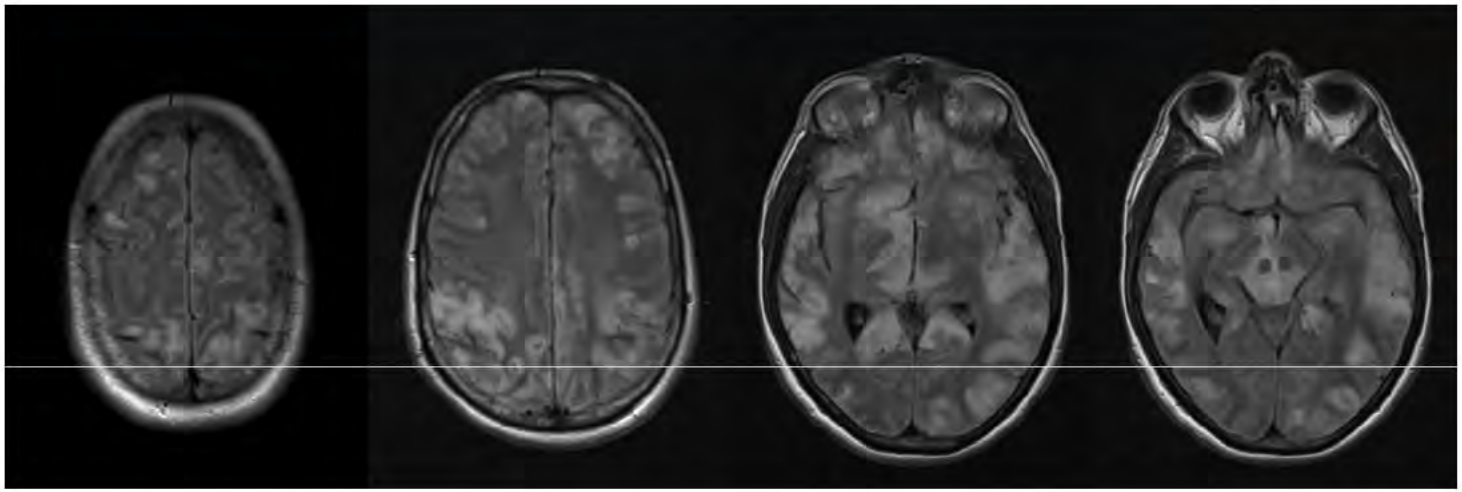
Selvey *et al*. Med J Aust 1995;162:642-5
O'Sullivan *et al*. Lancet 1997;349:93-5

Human clinical manifestations

Case	Date	Exposure to infected horses	Clinical syndrome	Outcome
4: Veterinarian	Nov 2004	Performed necropsy	'Influenza-like' illness	Recovery, no relapse
5: 33-yo Veterinarian	July 2008	Respiratory secretions, performed necropsy	Acute encephalitis	Died (day 31 illness)
6: 21-yo Veterinary nurse	July 2008	Respiratory secretions	Acute encephalitis	Recovery, persisting neurological deficits
7: 51-yo Veterinarian	August 2009	Respiratory secretions	Acute encephalitis	Died (day 19 illness)

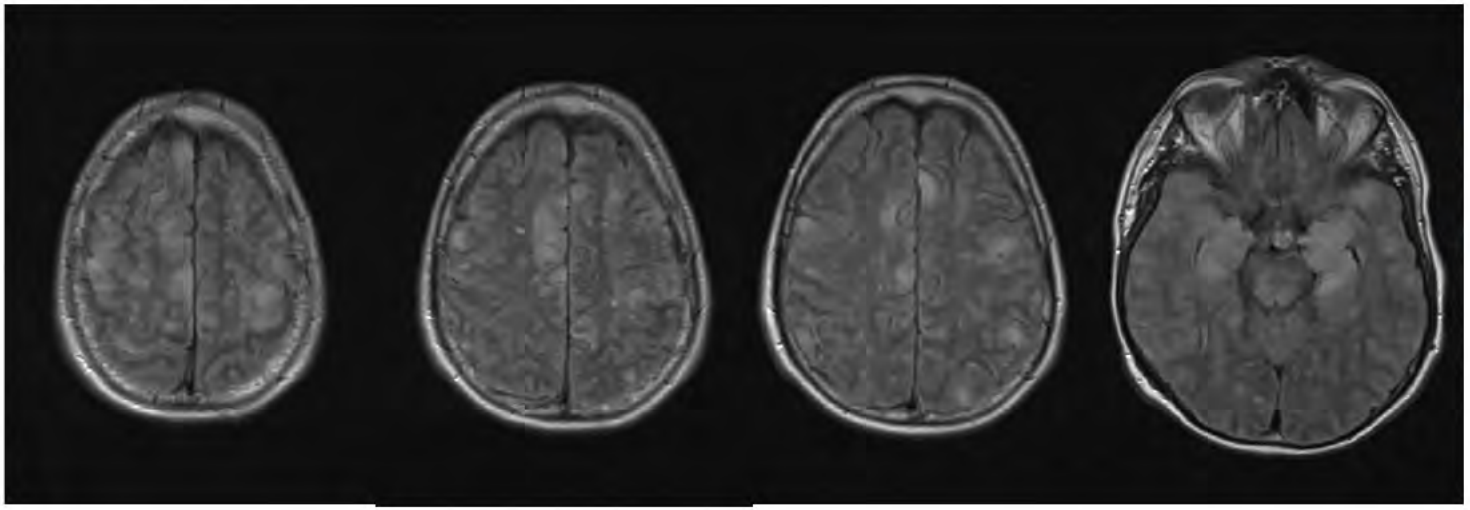
Hanna *et al*. Med J Aust 2006;562-4
Playford *et al*. Emerg Infect Dis 2010;16:219-23

Neuro-radiological manifestations



Case 6: day 25 (T2 FLAIR):

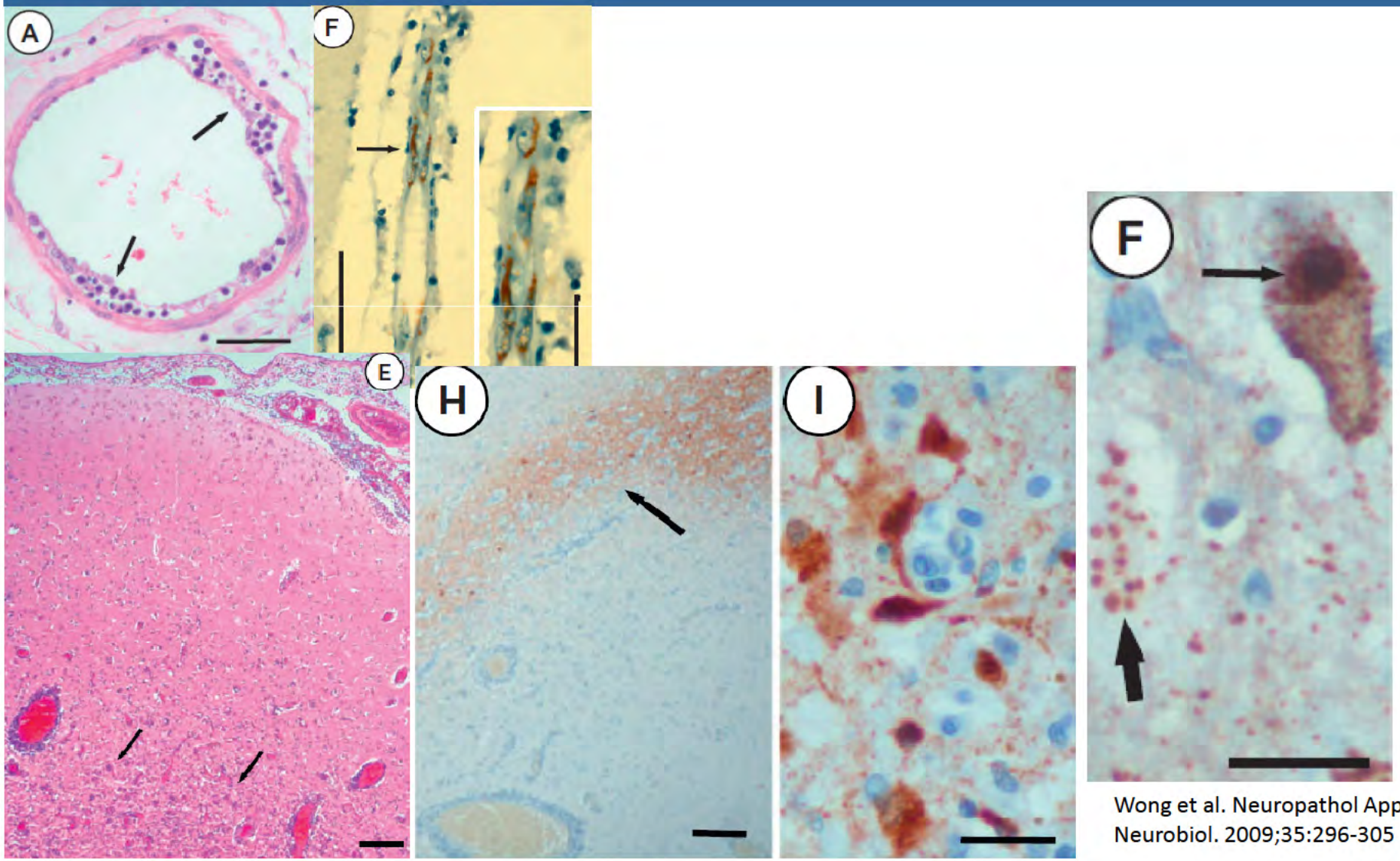
Innumerable cortical, subcortical and midbrain hyperintense foci



Case 7: day 9 (T2 FLAIR):

Extensive multifocal cerebral & brainstem hyperintensities

Histopathological findings



Wong et al. Neuropathol Appl Neurobiol. 2009;35:296-305

Human HeV infections
Summary

	No. human cases	No. deaths
Self-limited 'influenza-like' illness	2	0
Multi-organ failure with predominant pulmonary involvement	1	1
Aseptic meningitis with late relapsing encephalitis	1	1
Acute encephalitis	3	2
Total	**7**	**4**

- Incubation period:
  - Range, 5-21 days
- Exposures:
  - All experienced close unprotected mucosal &/or cutaneous exposures to respiratory secretions &/or blood from horses with unrecognised infection
  - No evidence of asymptomatic seroconversion

Public Health investigations
Follow-up of humans exposed to equine HeV

Outbreak	Number exposed	PPE use	Infection
Hendra, 1994	8 close contact with infected horses	0%	2 (25%)
Thornlands, 2008	14 staff with “high risk” exposures	7%	2 (14%)
Cawarral, 2009	4 stud workers with “high risk” exposures	0%	1 (25%)

Selvey *et al*. Med J Aust 1995;162:642-5 ; Playford *et al*. Emerg Infect Dis 2010;16:219-23

6. EXPOSURE ASSESSMENT table		
Nature and magnitude of exposures	**Assessment**	**Management**
No exposure to dermis and/or mucous membranes	Nil	Reassurance Information Serology Other testing Referred to GP Other
Slight to extensive exposures to intact dermis on <3 occasions	Negligible	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Adequate and consistent use of appropriate hand hygiene with intact skin and only skin contact	Negligible	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Adequate and consistent use of PPE without breaches	Negligible	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Slight to extensive exposures to intact dermis on 3 or more occasions	Low	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Slight exposures to mucous membranes or uncovered wounds on 1 occasion	Low	Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Moderate exposures to mucous membranes or uncovered wounds on 1 occasion	Medium	Initial assessment Final assessment after discussion with IDP Reassurance Information Serology Other testing Referred to GP Restriction, donation Other
Extensive exposures to mucous membranes and/or uncovered wounds and/or needlestick injury on single or multiple occasions without adequate PPE e.g. kissing horse on muzzle, being drenched with oral or respiratory secretions, undertook respiratory tract procedures such as endoscopy or nasal lavage, performed or assisted with post mortem	High	Initial assessment Final assessment after discussion with IDP Referred Contact to IDP Reassurance Information Serology Other testing Referred to GP Restriction, donation Other

Exposure assessment

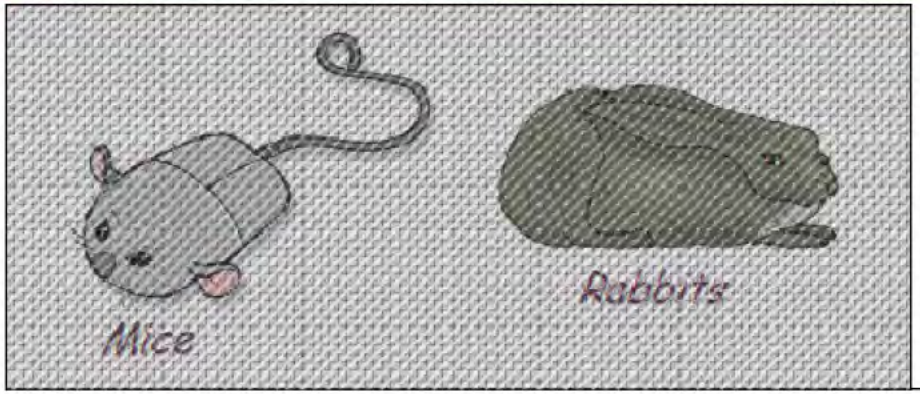
- "Medium" level exposures:
  - Moderate exposures to mucous membranes on one occasion
- "High" level exposures:
  - Extensive exposures to mucous membranes on multiple occasions
- Consideration for post exposure immunoprophylaxis

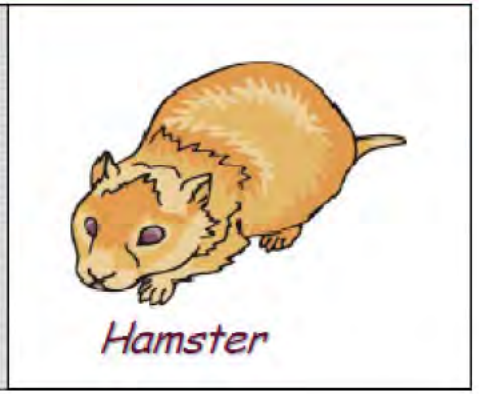
Prevention of human HeV infection

1. Standard precautions for equine contact
2. Routine use of precautions for procedures involving nose and respiratory tract
3. Increased precautions during procedures involving sick horses
4. Minimising contact with sick horses until Hendra virus excluded
5. Keeping horses and water/feed troughs away from areas where contact with bat excreta likely
6. Routine hand hygiene after contact with horses

Animal Models of Nipah and Hendra Virus Pathogenesis

Food and Drug Administration (FDA)
"Animal Rule" (21 CFR 314 Subpart I)



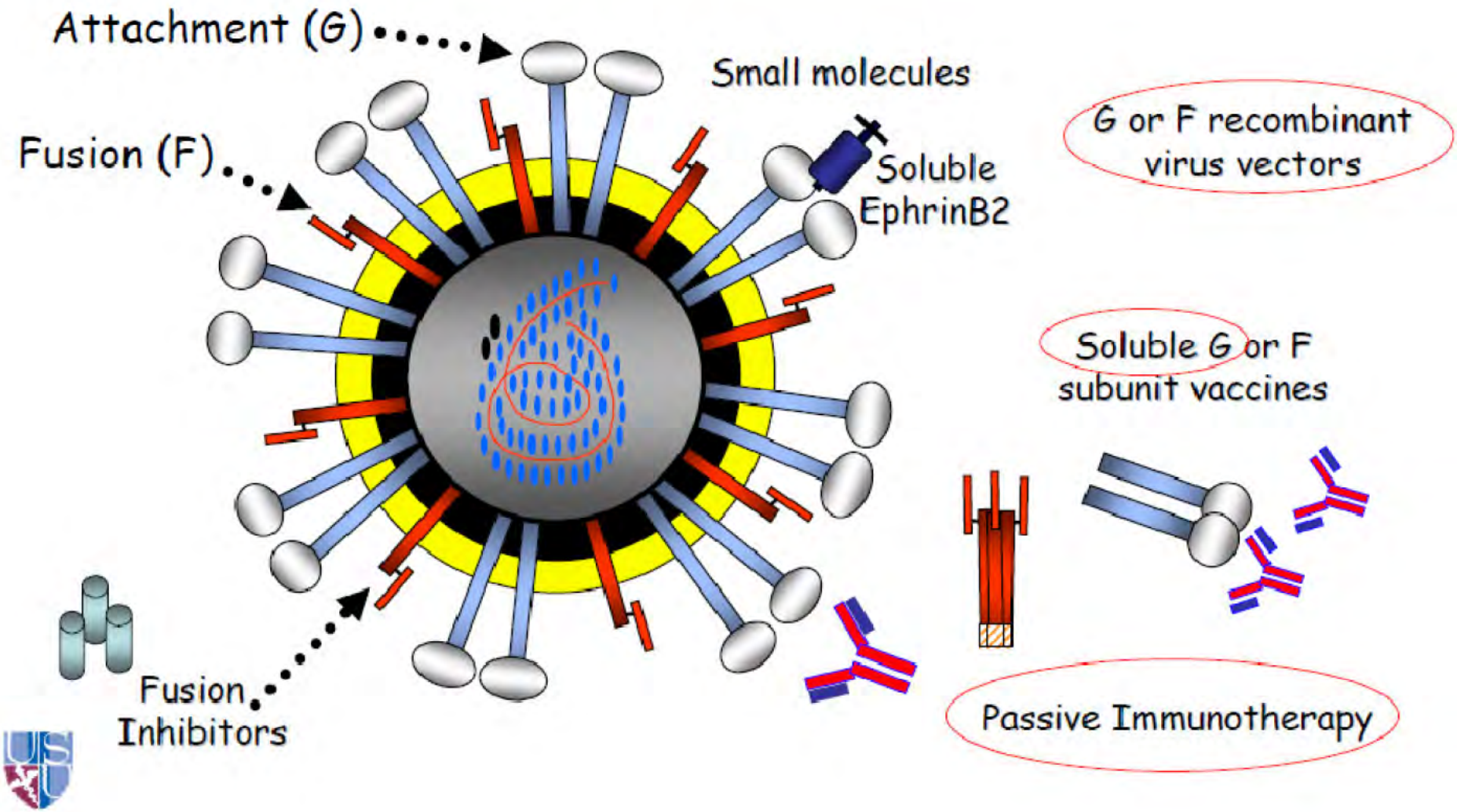


Ribavirin/chloroquine
Animal models

- Ribavirin:
  - AGM/HeV model
  - Golden hamster/NiV model
    - *Delayed but did not prevent death*
- Chloroquine:
  - Ferret/NiV model
    - *No benefit*
- Chloroquine +/- Ribavirin:
  - Golden hamster/HeV & NiV model:
    - *Ribavirin: delayed NiV death by ~5 days*
    - *Chloroquine or Ribavirin/Chloroquine: no benefit*

Rockx et al. J Virol 2010 (in press); Geogres-Coubot et al. Antimicrob Agents Chemother 2006;50:1768-72; Pallister et al. J Virol 2009;83:11979-82; Freiberg et al. J Gen Virol 2010;91:765-72

Heninpavirus vaccines and therapeutics



Passive immunoprophylaxis for HeV/NiV

- Polyclonal Ab following NiV F and G-expressing rVV vaccination:
  - ***Protective***
- Murine mAb (to F and/or G) in Hamster/NiV & HeV models:
  - ***Protective***

TABLE 3. Titration of the in vivo protection of anti-NiV MAbs[a]

MAb	Quantity of MAb administered (μg)	% of surviving animals	Mean time of death (days)
None (control)		0	7.5
Nip GIP 1.7 (anti-NiV.G)	112	100	
	1.12	100	
	0.12	25	10.5
	0.012	25	12.5
	0.0012	25	9.5
Nip GIP 35 (anti-NiV.F)	180	100	
	1.8	50	11.5
	0.18	0	7.75
	0.0.18	0	6.75
	0.0018	0	6.75

[a] Hamsters (four animals per group) were given dilutions of MAbs 24 h prior to and 1 h after receiving a lethal challenge of NiV.

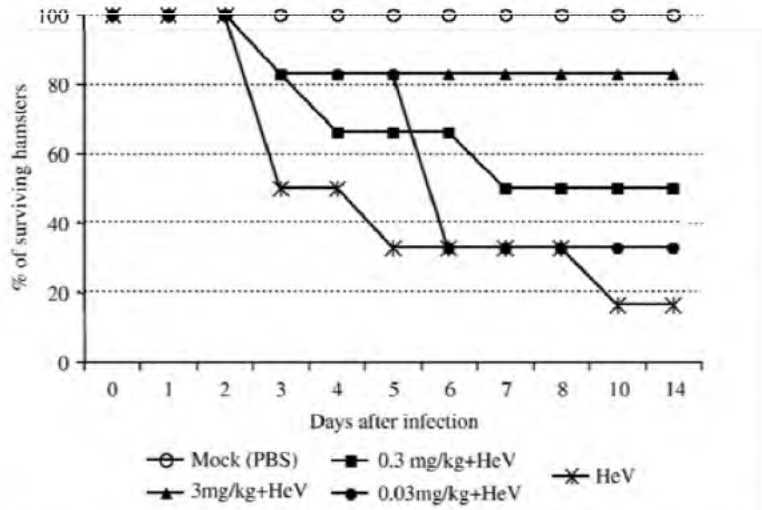
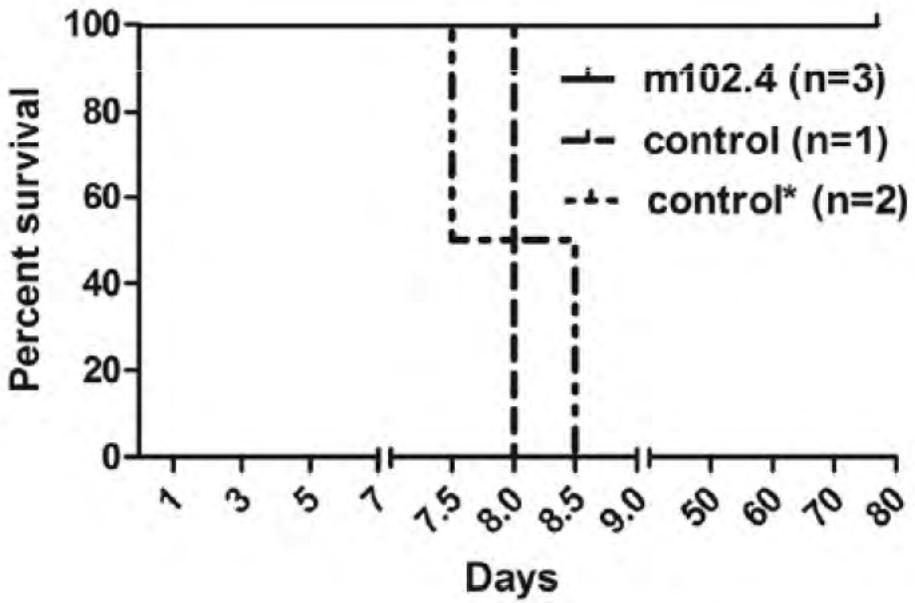


Fig. 4. Passive protection against HeV in hamster using three concentrations of the MAb anti-NiV-F Nip GIP21. Groups of 6 hamsters were inoculated i.p. with indicated concentrations of MAb or PBS, 1 h prior to infection with 10^3 PFU of HeV and followed daily for the development of clinical symptoms.

Guillame et al. J Virol 2006;80:1972-8; Guillaume et al. Virology 2009;387:459-65

Passive immunoprophylaxis
Human mAb

- Candidate mAbs identified through screening naive human Ab library
- m102.4 with high affinity for both HeV & HiV
- Ferret/NiV model:
  - Protective 24 hours pre-challenge
  - t½=3.5 days
- AGM/HeV model
  - Protective 10 hours pre-/3 days post- challenge
  - t½=10-12.5 days



Zhu et al. J Virol 2006;80:891-9; Zhu et al. J Infect Dis 2008;197:846-53; Bossart et al. PLOS Pathogens 2009;5:e1000642

m102.4: use in humans

- 2009: single patient with established HeV encephalitis
  - 100 mg (<1 mg/kg) mAb available
  - No overt reaction/toxicity
  - No efficacy
- 2010: 2 persons with mod-high exposures
  - ~18 mg/kg mAb infused iv to both
  - Significant systemic reactions (fevers, rigors, myalgias): required prolonged infusion (~12 hours)
  - No evidence HeV infection (negative PCR, no anti-F seroconversion to date)
  - t½~20 days

m102.4: current situation

- Supply:
  - Produced by AIBN at UQ: ~30g available
- Unanswered questions:
  - Accuracy of risk assessment post-exposure
  - Is there a therapeutic window period post-exposure?
  - Could mAb be effective at onset of initial viral replication or does it need to be given prior?
  - Safety: need for pre-clinical assessment and phase 1 study

Human health research priorities

- Establish safety of mAb
  - Pre-clinical & phase 1 human studies
- Establish efficacy window
  - Further animal model studies
- Refinement of exposure – risk assessment:
  - Pooling available data 1994-2011
  - Standardisation of approach across jurisdictions