Emerging Zoonoses: Nipah and Hendra viruses

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Histogram of the phosphoprotein gene of members of the subfamily Paramyxovirinae

Hendra and Nipah viruses

• History of previous outbreaks
• Reservoirs of viruses
• Clinical features in human
• Diagnosis and Treatment
• Transmission and Epidemiology
• Disease in horses and pigs
• Prevention and Control
In 1995, a 36yo farmer died of severe encephalitis in Mackay, Queensland.

Two horses died a year before of unknown infection (one of pneumonia, the other of acute neurological illness) retrospectively Hendra-confirmed.

He had assist at their post-mortem examination and had retrospective serologic evidence of Hendra infection at that time.
History of Hendra outbreaks, Australia

Eaton 2005
February 2010

History of Nipah outbreaks - Malaysia - 1999

Outbreak of viral encephalitis in Malaysia:
• Disease in humans (mostly pig farmers) with cases described as beginning in October 1998
• Parallel disease in pigs, but not initially reported nor well described
• Japanese encephalitis diagnosed as the etiology of the disease in humans and pigs
• March 1999. CSF from patients from Negeri Sembilan: yields cytopathic agent. EM–paramyxovirus like morphology on thin section. 12/13 patients positive by Hendra IgM capture. IHC on frozen brain positive for Hendra
• RT-PCR is positive with degenerate paramyxovirus P-protein primers, sequence is Hendra-like but distinct

History of Nipah outbreaks

• In 1999, Singapore’s importation of infected pigs from Malaysia. 22 human cases and one death. Of these, 12 (54±6%) were symptomatic, 9 presented with encephalitis, 2 with pneumonia and 1 with both encephalitis and pneumonia. Stopped with pig import ban from Malaysia.
• Since 2001, 10 outbreaks in Bangladesh, 2 in West Bengal, India.
• Since discovery, 480 human cases including 251 deaths

Eaton 2005
February 2010
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Reservoirs of viruses

Hendra

- fruit bats identified as the natural host in 1996.
- antibodies in all 4 species (20-50%).
- antibodies across the geographic range.
- no attributed clinical disease in flying foxes.
- antibodies in archive samples.
Reservoirs of viruses
Nipah Malaysia

<table>
<thead>
<tr>
<th>Species</th>
<th>Tested</th>
<th>Nipah SNT Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pteropus vampyrus</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Pteropus hypomalenus</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Cynopterus brachyolitis</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>Cynopterus horsfieldi</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Rousettus amplexicaudatus</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Eonycteris spelaea</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>Macroglossus sobrinus</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Balionycteris maculata</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Megaerops ecaudatus</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Scotophuilus kuhli</td>
<td>58</td>
<td>0*</td>
</tr>
<tr>
<td>Rhinolophus spp.</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Taphozous melanopogon</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Hippeosiderus bicolor</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Total of ~310 bats
KB Chua has isolated Nipah virus from Pteropus hypomalenus

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Clinical features - Hendra

- All have unprotected contact with infected horses
- Incubation period 5-14 days
- All cases symptomatic (4/7 died)
- All start with “flu-like” syndrome: fever, headache, myalgias, sore-throat, dry cough
- Neurological manifestations indicative of bad prognosis
- Multi-organ failure and death

Mild case in a veterinarian (Hanna et al. Med J Aust 2006;562-4)
- Extensive exposure to horse’s blood & body fluids during necropsy on horse with acute febrile illness with respiratory and pre-terminal neurological manifestations
- Onset 7 days later: febrile illness with cough, pharyngitis, cervical lymphadenopathy
- Recovered ~8 days later
- Seroconversion to HeV on day 14 of illness
- No clinical evidence of relapse

33-year-old equine veterinarian (Playford et al. Emerg Infect Dis 2009 (in press))
- Performed necropsy and nasal cavity lavage on infected horses (16 and 9 days previously)
- Day 2 illness: Presented with “flu-like” illness, fevers, mild neutropenia & thrombocytopenia
- NPA/serum: RT-PCR-positive for HeV; – NPA: RT-PCR-negative for respiratory viruses
- Day 3–4: Adrenocortical
- Day 5: Drowsy, confused, ptosis, ataxia, dysarthria
- MRI: multifocal pontine & cortical lesions
- DWI: hyperintense foci c/w infarction
- CSF: Leukocytes <5×10^6/L, protein 600 mg/L, HeV RT-PCR-positive
- EEG: Bilateral slow wave activity
- Commenced on iv Ribavirin (30 mg/kg, then 15 mg/kg q6h)
- Days 6–31: Progressive neurological deterioration: Generalised partial tonic-clonic seizure (day 10); Ventilated (day 11); Ribavirin ceased because of haemolytic anaemia (day 16); Sluggish reactive pupils, minimal responsiveness off sedation despite seizure control (day 19 on)
- MRIs: Innumerable widespread multifocal lesions on T2 FLAIR; lesions c/w infarction on DWI
- EEGs: absent stable rhythm, periodic sharp waves, severe diffuse encephalopathy
- Day 31: Death
Clinical features - Hendra

Day 5

Day 18

Day 25

Clinical features – Nipah
Malaysia

- Febrile illness - 4-7 days duration
- Early respiratory signs?
- Headache, drowsiness, slurred speech, loss of cognition, coma
- Neurological signs suggest mid-brain, pons lesions
- Pathology: diffuse focal lesions of CNS
- Mortality ~36% of those hospitalized (105/285)
- There were subclinical infections

Admission Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Median</th>
<th>Range</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (x1000/mm3)</td>
<td>5.2</td>
<td>1.2 – 14.7</td>
<td>(4.5-11.0)</td>
</tr>
<tr>
<td>Platelet (x1000/mm3)</td>
<td>141</td>
<td>8 - 357</td>
<td>(150-400)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9</td>
<td>0.4 - 5.0</td>
<td>(0.7-1.5)</td>
</tr>
<tr>
<td>CSF WBC (# /cu mm)</td>
<td>2</td>
<td>0-1250</td>
<td>(0-10)</td>
</tr>
<tr>
<td>CSF protein (mg/dL)</td>
<td>67</td>
<td>15 - 335</td>
<td>(15-45)</td>
</tr>
</tbody>
</table>
Clinical features of Nipah virus encephalitis
Goh et al NEJM 2000;342:1229

Clinical features at presentation (n=94)

- Fever 97%
- Headache 65%
- Dizziness 36%
- Vomiting 27%
- Reduced consciousness 21%
- Nonproductive cough 14%
- Myalgia 12%
- Focal neurological signs 10%

Neurological characteristics (n=94)

- Absent or reduced reflexes 56%
- Impaired consciousness 55%
- Abnormal pupils 52%
- Tachycardia 39%
- Abnormal doll’s eye reflex 39%
- Segmental myoclonus 32%
- Meningism 28%
- Seizures 23%
- Nystagmus 16%
- Cerebellar signs 9%

Factors associated with prognosis
Goh et al. NEJM 2000;342:1229

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>DEATH (N=30)</th>
<th>SURVIVAL (N=64)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age — yr</td>
<td>40.9</td>
<td>35.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Vomiting — no. (%)</td>
<td>12 (40)</td>
<td>13 (20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean lowest Glasgow Coma scores</td>
<td>6.8</td>
<td>12.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Segmental myoclonus — no. (%)</td>
<td>26 (87)</td>
<td>10 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal doll’s eye reflex — no. (%)</td>
<td>25 (82)</td>
<td>15 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal pupils — no. (%)</td>
<td>29 (97)</td>
<td>20 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>23 (77)</td>
<td>14 (22)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tachycardia — no. (%)</td>
<td>28 (93)</td>
<td>8 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absent or reduced reflexes — no. (%)</td>
<td>22 (73)</td>
<td>31 (48)</td>
<td>0.02</td>
</tr>
<tr>
<td>Seizures — no. (%)</td>
<td>12 (40)</td>
<td>10 (16)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean AST level at admission — U/liter</td>
<td>87</td>
<td>34.4</td>
<td>0.051</td>
</tr>
<tr>
<td>Mean ALT level at admission — U/liter</td>
<td>54.2</td>
<td>53.6</td>
<td>0.896</td>
</tr>
<tr>
<td>Mean platelet count at admission — per mm3</td>
<td>151,000</td>
<td>197,000</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Relapsed and late-onset Nipah encephalitis

Relapsed encephalitis was seen in 15 (9%) of acute encephalitis survivors
Late-onset encephalitis was seen in 10 (3.4%) of those with previous non-encephalitic or asymptomatic Nipah infection
Mean duration from initial infection: 13 months (up to 4 ½ years)
3/25 patients had a second neurological episode

Immunohistochemistry - Nipah

Long-term neurological and functional outcome in Nipah virus infection

Of the survivors of acute Nipah infection in Bangladesh
# 21/22 had disabling fatigue, with medium duration of 5 months;
# 3 patients continued to have profound fatigue 2 years after infection
# >50% of those <16 years had Behavioral abnormalities
Hendra and Nipah viruses

- History of previous outbreaks
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- **Diagnosis and Treatment**
- Transmission and Epidemiology
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Laboratory diagnosis

“BSL-4 agent”

<table>
<thead>
<tr>
<th>Sample</th>
<th>PCR</th>
<th>Isolation</th>
<th>IHC</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/T Swab</td>
<td>+*</td>
<td>+*</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Urine</td>
<td>+*</td>
<td>+*</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Blood</td>
<td>+/-</td>
<td>-</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>CSF</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Tissues</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Positivity decrease when Ab appears

Treatment Potential

**prophylactic/therapeutic modalities**

- Ribavirin Nipah/Hendra
- Chloroquine
- Passive immunotherapy
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Hendra virus: transmission

Risk of spillover from bats

Probability of spillover from any given colony depends on
• the proportion of susceptible flying foxes,
• the colony size,
• the presence of infection,
plus
• the number and density of horses,
• the number and density of flying foxes,
• management of the horses,
• the virus strain/virus dose/route of infection?
Nipah virus: transmission

Cases of Encephalitis in Malaysia
September 1998 to May 1999
National Swine Surveillance

- Limited period (90 days)
- All premises sampled
  - Based on high morbidity data
  - 15 sows
  - 2 samples (at least 21 days apart)
- Abattoir sampling
- Active disease discovery
- Human case discovery
- Cull infected premises

Results of Phase II Nat. Swine Surveillance

A total of 889 farms were tested

50 farms were found to have evidence of Nipah infection by the prearranged criteria

Farms culled

Epidemiology Nipah Malaysia

- Spread
  - Movement of infected swine
- Transmission in swine:
  - Very transmissible in modern husbandry setting: crowding
  - Virus maintenance in swine
  - Continuous transmission?
  - Persistent infections?
Investigations Nipah Malaysia

- Risk factors:
  - Direct live infected pig contact
  - Non-encephalitic/non-clinical infections
  - Virus molecular epidemiology
    - Pigs and human cases: identical sequence
    - Nosocomial infections? No
  - Natural reservoir?
  - Other species:
    - Dogs, cats, horses: but non-spreading
    - Rodents, birds, insectivores: none or very low

Risk factors & transmission of Nipah in Bangladesh

<table>
<thead>
<tr>
<th>Year</th>
<th>Districts</th>
<th>Transmission and risk factors</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Meherpur</td>
<td>Caring or living with a case</td>
<td>OR 7.6; 95% CI 2.2-27.7</td>
</tr>
<tr>
<td>2003</td>
<td>Naogaon</td>
<td>Close proximity with pig herds</td>
<td>OR 6.1; 95% CI 1.4-25.3</td>
</tr>
<tr>
<td>2004</td>
<td>Rajshahi</td>
<td>Climbing trees</td>
<td>OR 8.2; 95% CI 1.3-52.8</td>
</tr>
<tr>
<td>2008</td>
<td>Faridpur</td>
<td>Touching a Nipah patient</td>
<td>RR 15.0, 95% CI 4.6, 55</td>
</tr>
<tr>
<td>2005</td>
<td>Tangail</td>
<td>Drinking raw date palm juice</td>
<td>OR 7.0, 95% CI 1.6-31, p&lt;0.01</td>
</tr>
<tr>
<td>2007</td>
<td>Thakurgaon</td>
<td>Remaining in the same room with</td>
<td>OR 87.6, 95% CI 4.4-7.44</td>
</tr>
<tr>
<td>2007</td>
<td>Kuribari</td>
<td>Person to person</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>2008</td>
<td>Manikganj</td>
<td>Drinking raw date palm juice</td>
<td>Adjusted OR 18, 95% CI</td>
</tr>
<tr>
<td></td>
<td>and Rajbari</td>
<td>and Rajbari</td>
<td>2.2 = x, p&lt;0.005</td>
</tr>
</tbody>
</table>

Bangladesh Epidemiology

- Person-to-person transmission
  - 5 of 11 clusters, involved ranging from 1 to 5 generations
  - Study conducted to reduce the risk of Nipah virus transmission
    - Nipah virus isolated from saliva and urine
    - Nipah infection associated with close contact of patients
    - Handwashing is protective
- Superspreaders
  - Palm sap transmission
    - Epidemiology date palm sap collection
    - Explore spraying techniques to interrupt bats in processing date palm sap
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Hendra disease in horses

Respiratory HeV
- Peracute or acute illness
- Frothy nasal discharge
- Facial oedema
- Body temperature > 40 C
- Elevated heart rate (>90 beats/minute)

Neurological HeV (seen recently in Australia)
- Mild focal neurological signs, including muscle twitching
- Ataxia
- Head tilt, facial nerve paralysis
- Elevated body temperature
- Neurological signs may resolve

Nipah disease in swine

- Febrile respiratory disease predominates
- Labored or forced breathing
- “One-mile” cough
- CNS disease much rarer than in man
- Sudden death/neurological disease in sows and boars, some abortions reported
- Mortality 1-3%, morbidity ~100%
- Post-mortem changes primarily in lung, some CNS
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1. Control in domestic animals

- Routine cleaning & disinfection of pig farm/horse stable is expected to be effective in preventing infection
- Reducing the risk of bat-to-domestic animal transmission: bat proof buildings, bat exclusion strategy, fruit tree removal...
- Outbreak suspected: Quarantine animal premises ± euthanasia or culling of infected animal(s) Restrict/ ban animals movements
- Establish active animal health surveillance system for early warning for veterinary and human public health authorities.

2. Reducing risk of infection in people

- Reduce risk of bats-to-human transmission: Protect collection process of date palm juice (bamboo) Wash & peel fruits thoroughly
- Reduce risk of human-to-human transmission: Avoid or minimize physical contact with ill patient Hand hygiene + use of personal protective equipment (PPE)
- Reduce risk of domestic animal-to-human transmission: Avoid or minimize contact with ill or dead pig, horse Hand hygiene + use of personal protective equipment (PPE) Particularly important in veterinary practices (caries, necropsies)
Social Mobilization and Communication

- Prevention: what should be the key messages:
  - Exposure to bats
  - Exposure to sick animals
  - Home care
  - Funerals?
- Guidelines/trainings for specialized categories
  - Health care workers
  - Veterinarians
  - Farmers
  - Wildlife experts