Nipah/Hendra – Understanding the links between human and veterinary emerging diseases

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**ZOONOSES: an import risk for disease emergence**

<table>
<thead>
<tr>
<th>Infectious organism</th>
<th>Human pathogen</th>
<th>Zoonoses</th>
<th>Emerging diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=1709)</td>
<td>(N=832)</td>
<td>(N=156)</td>
</tr>
<tr>
<td>Viruses/Prions</td>
<td>507 (30%)</td>
<td>183 (22%)</td>
<td>64 (41%)</td>
</tr>
<tr>
<td>Bacteria/Rickettsia</td>
<td>541 (32%)</td>
<td>250 (30%)</td>
<td>48 (31%)</td>
</tr>
<tr>
<td>Fungi</td>
<td>309 (18%)</td>
<td>83 (10%)</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Helminths</td>
<td>286 (17%)</td>
<td>275 (33%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Protozoa</td>
<td>60 (3%)</td>
<td>41 (5%)</td>
<td>19 (12%)</td>
</tr>
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</table>

Animals have been, are and will constitute an important source of infectious diseases for humans:

- About half of the human pathogens are zoonotic and 9% are emerging

- The three most devastating pandemics in history were zoonotic (Plague, Spanish Influenza, HIV/AIDS)

- About 75% of the recent emerging pathogens are zoonotic (WNV, SARS, Nipah/Hendra, ...)

Overall, zoonotic pathogens are more than 3 times more likely to be associated with emerging diseases than non-zoonotic pathogens.
Transmission

- Zoonotic transmission includes:
  - Wildlife reservoirs transmitting directly to humans: rabies, West Nile virus...
  - Transmission from a wildlife reservoir to humans via domestic animals: influenzas, rabies, Hendra and Nipah, brucellosis, tuberculosis
  - Transmission to humans via the Food chain (Food Safety): salmonella, E. coli O157,

(Lloyd-Smith J.O. et al. (2009) Science 326: 1362-1367)
Diagram of zoonotic transmission dynamics


Vaccine Technology III, Mexico, 2010
Emergence of new agents

• Increased global travel: e.g. influenza’s – Avian/swine

• Relaxation of veterinary regulations: e.g. EIV outbreak in Australia in 2007

• Unpredictable effects of climate change: Bluetongue virus outbreak in Europe

• Urbanization and change in animal husbandry: HSF, PRRS and PCV-2 in swine

• The threat of intentional release...
The example of Nipah/Hendra

- Hendra and Nipah viruses are newly discovered zoonotic viruses first isolated from outbreaks in Australia (1994) and Malaysia (1998).

- The viruses are closely related and member of the *paramyxoviridae* family, genus *Henipahvirus*.

- The viruses cause severe disease in a variety of animal species, including humans, horses, pigs, dogs and cats.

- Both viruses are classified as BSL-4 pathogens and Nipah is on the list of select agents by the USDA.

*Eaton et al, 2006. Nature Reviews Microbiology*
Hendra outbreaks

- In September 1994, an outbreak of acute respiratory disease occurred in a group of horses outside Brisbane.
- 20 horses affected: 14 died (6 euthanized).
- Horses were tachypnoeic, tachycardic, ataxic, frothy nasal discharge, collapse – 7 deaths within 12 hours, (10 < 36 hours).
- Two people nursing the index case became infected, 1 died.
Hendra outbreaks

- Since 1994, Hendra has caused a few sporadic outbreaks in Australia, i.e., a total of 14 reported outbreaks involving ~40 horses and 7 humans
  - Case-fatality rate in horses: 80%
  - Case-fatality rate in humans: 57%. One patient presenting relapsed encephalitis long after the initial infection

- Equine cases occur mainly late winter/spring. Horse to horse transmission is not easy

- All human cases associated with close contact with affected horses (endoscopy, treating, nursing or post-mortem examination). Extremely low risk handling normal horses

- No human-to-human transmission reported
Nipah outbreaks

• Nipah emerged in 1998 in Malaysia and caused widespread panic because of the high mortality rate (40%) in people and the inability to control the disease initially.

• Pigs were the apparent source of infection among most human cases (farmers, abattoir workers). Pigs were frequently asymptomatic (silent spreaders).

• Subsequent outbreaks in Malaysia, India and Bangladesh in 2000-2008

• Human case-fatality rate 40-75%

• Human-to-human transmission of Nipah virus and no obvious direct link to infected livestock reported in later outbreaks.
Nipah Field Investigations - Malaysia
The Impact of the Outbreak

• Limited in geographic extension, but....

• The Malaysian outbreak caused considerable social disruptions and tremendous economic loss to an important pig industry.
  - Nearly 1 million pigs culled (58 M$)
  - Loss of the capital infrastructure on farms
  - Loss of employment - 36,000 jobs
  - Loss of export income - 120 M$
The Impact of the Outbreak

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Where did the virus come from?

- Pteropid bats (fruit bats) are believed to be the natural reservoir hosts. Different bat species for Nipah and Hendra

- Seroprevalence varies between bat colonies (2–50%). Suggests non-lethal infection in bats

- Detected in bat secretions (abortions & urine)

- No definitive data on bat-to-bat spread

- Spill-over transmission to pigs/horses is likely to occur through contaminated water and feed
Global Distribution of fruit bats

Courtesy: CSIRO
Antibody to Hendra has been detected in all 4 species of fruit bats indigenous to Australia. Equine cases occur mainly late winter/spring Associated with bat breeding season?

Influx of more than 130,000 bats into Victoria since early 2010 attributed to wet weather conditions in Queensland.
Transmission cycle

Hendra virus

Spill over

$R_o < 1$
Transmission cycle

Nipah virus

$R_0 > 1$

Spill over

$R_0 > 1$

Spill over
Management of the disease

- The following counter measurements are important
  
  - Surveillance: first line of defense. Very often relies on reporting of clinical disease in populations at risk, which is not very reliable
  
  - Culling: stop spread of virus
  
  - Vaccination: no commercial vaccines are available today
  
  - Diagnosis: stall-site (point-of-care) diagnostic tests are needed but not yet available
Vaccination

- Vaccination remains a primary method for the effective prevention and control of Nipah/Hendra

- The role of Manufactures for a **timely** supply of **affordable** and **fit-for-purpose** vaccines is pivotal

- Key to risk management is communication and co-operation through every sector of the industry.

- Several initiatives are ongoing....
Challenges and constraints

- The development of a human vaccine is likely to be expensive and long range making it uneconomical for any pharmaceutical company to undertake. Veterinary vaccines should be considered.

- Competition for assigned R&D resources

- Need for high containment facilities to develop and produce vaccine

- Scale up and transfer to Manufacturing

- Availability of BSL4 animal test facilities for testing of vaccines

The use of well characterized vaccine platforms will alleviate some of these issues.
# Potential available platforms

## Replicating vectors

### Viruses
- **Poxviruses (vaccinia)**
- Adenoviruses
- **Herpes viruses (HVT)**

### Bacteria
- Mycobacteria (BCG)
- Salmonella

### DNA vectors
- Replicons

### RNA vectors
- Replicons

## Non replicating vectors

### Viruses
- (Avi)Poxviruses (ALVAC)
- Adenoviruses (E1 del)
- Herpesviruses (gD del)

### DNA vaccines
- Plasmids (Melanoma; WNV)
- Linear expression cassettes

### Expression systems
- Baculovirus (PCV-2)
- Plant expression
- Peptides

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**Technologies having at least one example of registered vaccine**
The use of ALVAC as a vector

- The canarypox virus vector originates from an attenuated vaccine strain for canaries
- Large genome, easily manipulated and genetically stable
- Real technology platform used for commercial vaccines in dogs, cats, ferrets and horses and has potential in humans
- Non replicative vector in mammals

“Single hit infection”
After vaccination the vector infects and instructs the cell to produce the protective proteins which in turn are presented to the immune system in a way that closely mimics natural infection (authentic expression). The vaccine induces both B and T cell immunity.
ALVAC is a true technology platform

R&D
• Rapid generation of new constructs (strong expertise)
• No handling of dangerous pathogens (WNV, H5N1, NiV..) through the use of synthetic genes

Manufacturing
• Same manufacturing process for all recombinants: simple process with high batch-to-batch consistency which is easy to scale up
• Standardized batch release test

Regulatory
• Known technology.
ALVAC: a commercial success
Nipah vaccine candidates

- Several vaccine platforms have been tested successfully for efficacy in animal models
  - Recombinant vaccinia vaccine expressing G or F of NiV virus (Guillaume et al. J. Virol. 78, 2004). Regulatory acceptance?
  - Subunit vaccine containing soluble G protein of NiV purified from recombinant vaccinia infected cells (Mungall et al. J. Virol. 80, 2006). Scalability?
  - Recombinant canarypox (ALVAC) vaccine expressing G or F of NiV virus
Proof of concept ALVAC-NiV constructs

- Pigs were vaccinated twice IM at 14 days interval and challenged on D28 by intranasal inoculation of NiV (2.5 x 10⁸ PFU)

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<th>V1</th>
<th>V2</th>
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<tr>
<td>Treatment</td>
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<tr>
<td>1 ALVAC F</td>
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<tr>
<td>2 ALVAC G</td>
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</tr>
<tr>
<td>3 ALVAC G + F</td>
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<tr>
<td>4 Controls</td>
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</table>

Treatment groups (4 pigs per group)
1 ALVAC F
2 ALVAC G
3 ALVAC G + F
4 Controls

ALVAC-F
ALVAC-G
ALVAC G + F
Recombinant Nipah Virus Vaccines Protect Pigs against Challenge

Hana M. Weingartl,1,2,* Yohannes Berhane,1 Jeff L. Caswell,3 Sheena Loosmore,4 Jean-Christophe Audonnet,5 James A. Roth,6 and Markus Czub2,7

NCFAD, CFIA, Winnipeg, Canada1; NML, PHAC, Winnipeg, Canada7; Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada2; Department of Pathobiology, University of Guelph, Guelph, Canada3; College of Veterinary Medicine, Iowa State University, Ames, Iowa6; Sanofi Pasteur, Toronto, Canada4; and Merial SAS, Lyon, France5
Virus Isolation Post-Challenge (PFU/ml)

<table>
<thead>
<tr>
<th>C</th>
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<thead>
<tr>
<th>C</th>
<th>Brain</th>
<th>Olfactory Bulb</th>
<th>Trigeminal ganglion</th>
<th>Turbinate</th>
<th>Trachea</th>
<th>Submand LNN</th>
<th>Bronch. LNN</th>
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<td>45</td>
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- Vaccination led to the development of high antibody levels
- Vaccination with ALVAC-NiV prevented virus replication and virus shedding
- Combined vaccination with both G and F induced the best protection

*Courtesy Wiengartl*
Conclusions

- Zoonotic pathogens constitute an important risk for emerging diseases in man

- Vaccination, together with management measures, remains the primary method for the effective prevention and control of emerging diseases

- Well established vaccine platforms will facilitate development and reduce time to market

- The example of Nipah/Hendra shows that effective control is the shared responsibility of Governments, Industry and stakeholders

- An effective vaccine against Nipah/Hendra is within reach....
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