Equine Influenza—Recent Developments

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Equine influenza virus

Type A

Two subtypes:
Equine-1 (H7N7) extinct?
Equine-2 (H3N8) common.

The leading cause of acute infectious respiratory disease in horses in the USA -- 37%.
---Equine ‘98 NAHMS Study

Highly contagious
Variable morbidity
Very low mortality

Spread internationally— horses travel widely for performance or breeding purposes.
Equine flu is enzootic in most of the world. Typically low incidence. Most horses develop natural immunity.
Recent international transmissions of Equine-2 Influenza

- 1992 Hong Kong
- 1995 Dubai
- 1997 Philippine
- 2003 South Africa
Reference Laboratories for Equine Influenza

Responsibilities:

- Disease diagnosis and surveillance.
- Research on disease surveillance, diagnostic methods, vaccination.
- Technical consultation about the disease and its control.
- Production, testing, and distribution of diagnostic reagents.
OIE/WHO Expert Surveillance Panel confers annually to reconsider equine flu vaccine strains.

Panel includes:

• Heads of OIE reference labs for equine influenza in England, Germany, USA;

• Heads of WHO collaborating centers for influenza in lower animals in USA, UK;

• Equine influenza experts in strategic countries.
2007 equine flu outbreak in Japan

Equine flu-free since 1972.

Many horses are regularly vaccinated.

Flu detected August 15—Febrile racehorse
Detected by Espline IDK, confirmed by RT-PCR

Virus isolate: Ibaraki/07

Movement bans, race cancellations.

About 1500 horses affected.

Low incidence and severity of disease.

Espline IDK, Fujirebio Inc.
Equine Influenza in Australia 2007

Historically free from EI; vaccination NOT practiced.

2001–
• Over 672,000 registered horses, + 300,000 feral horses in AUS.

• ~100,000 are Thoroughbreds, including ~30,000 broodmares.

• NSW is home to 40% of registered horses & 40% of thoroughbreds.

• Racing was a $7.7 billion industry employing 240,000.

• Australia leads world in # thoroughbred owners per capita, # race courses & race clubs.

• 2000-3000 horses imported annually
### Timeline of events—Australia 2007 EI outbreak

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<tr>
<th>Date</th>
<th>Event Description</th>
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<td>7-8 Aug</td>
<td>52 horses arrive at Eastern Creek Quarantine Station, Sydney, New South Wales, from Japan, Ireland, UK, USA.</td>
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| 17 Aug | EI detected at Eastern Creek.  
Same day -- EI was confirmed by PCR in Japan.                                                                                               |
| 22 Aug | Sick horses seen at Centennial Parklands Equestrian Centre, Sydney. Confirmed as EI on 25 August.                                                   |
| 28 Aug | Movement bans initiated.  
Confirmed infected premises (IP) in NSW and QLD.                                                                                           |
| 17 Sept| Strategic vaccination program announced.  
Over 1000 IP in NSW and QLD.                                                                                                                    |
| 29 Sept| Containment zones established:  
Green (safe), Amber (buffer), Red (infected), Purple (high activity). Strategic vaccinations begun in Amber zones. |
| 25 Dec | Last reported cases.                                                                                                                             |
| March 08| NSW and QLD declared provisionally free of EI                                                                                                 |
Strategic vaccination campaign

• Administered by the Australian government
  - microchipping of recipients
  - private purchase of vaccine is illegal
• Aim is ERADICATION
  - movement controls are main weapon,
  - vaccination is secondary
  - vaccination will eventually be discontinued
• Concentrate on horses in AMBER (buffer) zones
  - plus responses to owner demands
• Single vaccine—Merial Proteq-Flu
  - recombinant canarypox with flu HA →
  - allows discrimination between vaccinates and infecteds by serology
Australia 2007 EI outbreak--Summary

• EI was confined to NSW and QLD by movement restrictions. No spread to other states.

• Mortality believed to be low but no statistics available.

• No spread to feral horses so far as is known.

• About 50,000 horses affected on about 7,000 premises.

• Vaccination will be continued through June 2008 (at least).

• Assuming no new cases, Australia can regain flu-free status on December 25, 2008.

• Direct cost of outbreak est. 100+million dollars (AUS) Indirect cost $1 billion?
How did the virus get into Australia?

The Sydney/2007 virus —

- broke through a quarantine system intended to prevent importation of infectious diseases.
- was transmitted to resident horses having no known contact with imported horses.
Most probable scenario—

- **INTRODUCTION**—likely from Japan on 8 August:
  --flu at Spotswood Quarantine Station too
  --sequence of seroconversions within Eastern Creek

- **AMPLIFICATION**—transmitted during PAQ to another imported horse with low antibody titers.

- **ESCAPE**—fomite transmission via clothing, gear? to a resident horse(s) in Sydney area, 13-14 August.

- **DISPERAL**—resident horse travels to Maitland event, 18-19 August →200 horses exposed.

Other scenarios—windborne, dogs at Eastern Creek, human international traveler—are considered unlikely.

Arrived from Japan 8 August

Susceptible-low Ab titer

Hypothetical Scenario for EI amplification
New quarantine measures for importation of horses into AUS

• Current vaccination, plus booster vaccination required between 14 and 21 days of entering PEQ.

• PCR testing for EI, 7 to 10 days apart in PEQ, last test within 4 days of departure, and PCR testing in PAQ on day 5. NZ has also added PCR.

• PAQ quarantine period extended to 21 days (from 14 days) --for horses imported permanently --where PEQ was in different premises but become intermingled.
PCR validation

- No RT-PCR for EI listed in OIE Manual of Diagnostic Tests.
- Japan uses Espline IDK, and the PCR method of Newton (Vet Rec 2006) to characterize HA.
- AHT uses ELISA, not PCR (yet).
- Gluck (U.B.) uses Directigen & real-time PCR for NP, M, HA.

AUS will accept any influenza PCR that is government-certified.
Characterization of influenza viruses
Antigenic comparison

Hemagglutinin amino acid sequence

influenza A/equine/South Africa/4/03 (H3N8)

Virus type  Host species  Geographic origin  Strain number  Year of isolation  Virus subtype
Evolution of Equine-2 Influenza Hemagglutinin

"American" lineage

"Eurasian" lineage
The virus

- Sequence analysis done at Australian Animal Health Laboratory.
- Matrix (M) gene: 99.6% similarity at amino acid level to Wisconsin/03 strain (H3N8).
- HA1 region of HA gene: close identity with Wisconsin/03 (99% similarity at amino acid level).

- Sydney/07, Ibaraki/1/07, & Pennsylvania/07 (isolated 8/29) are identical in HA1.
- Only 2 amino acid differences in HA1 between these and Wisconsin/03.
Recommendation of the OIE Expert Surveillance Panel, March 2004

Vaccines should be updated as follows:

- **“American”** lineage: a virus antigenically resembling [South Africa/03](#) (such as Ohio/03, Wisconsin/03).

- **“Eurasian”** lineage: a virus antigenically resembling [Newmarket/2/93](#) (still).

[Sydney/07](#) and [Ibaraki/07](#) are similar to Wisconsin/03.

Lessons

• Outbreak can be and was contained, but great disruption & cost.

• Flu is highly contagious. Possibility of fomite transmission —via hands, gear, trailers?
  STRICT QUARANTINE & DISINFECT!

• Spread by aerosols—what is minimum distance for safety? not documented over 35 m.

• Reinforces need to update vaccines.
Equine influenza outbreaks resulting from international transport

- 1992: Hong Kong
- 1995: Dubai
- 1997: Philippines
- 2003: South Africa
- 2007: Japan
- 2007: Australia
OIE/WHO Expert Surveillance Panel

- Heads of OIE reference labs for equine influenza in England, Germany, USA;
- Heads of WHO collaborating centers for influenza in lower animals in USA, UK;
- Equine influenza experts in strategic countries.

Added in 2008: Australia, Japan, Ireland
Equine influenza in the USA, 2007

- Virus isolated
- PCR or IDK positive
- Suspicious HI titers
- Negative results
- No information
Equine influenza activity 2007
as reported to the Expert Surveillance Panel

Where identified, all outbreaks were of American lineage virus.
What about the “Eurasian” lineage?

- Occasional isolations
- But no large outbreaks

“There is no requirement to update the European lineage H3N8 virus component. Current strains in use are A/eq/Suffolk/89, A/eq/Newmarket2/93, A/eq/Borlange/91.

“If companies are considering including European viruses they should consult with experts to establish the current situation and availability of recent isolates.”

(from the ESP January 2008 report)
What about Equine-1 (H7N7) influenza?

1992, 2nd OIE/WHO Consultation on equine influenza:
- No confirmed virus isolation since 1979.
- Occasional serological evidence open to question.

1999, 4th OIE/WHO Consultation on equine influenza:
- No epidemiological justification for retaining in vaccines.
- Recommended---manufacturers may drop equine-1 influenza from vaccines.

(Some vaccines still include equine-1 strain)

Still need to watch out for Equine-1 virus!
New USDA guidelines for EI vaccine strain updating

- H7N7 strains may be removed.
- Substitutions: up to 2 strain substitutions/subtype may be made to a licensed product; not less than approved minimum antigen content.
  -- Immunogenicity must be similar to approved product.
  -- Test in ≥6 naïve horses, or ≥10 acceptable lab animals at minimum age on label.
  -- Antibody GMT for new strain should be same as demonstrated for original product at same post-vaccination interval.
- Addition of new strains, same subtypes:
  -- Antigen content of old strains must not be decreased.
  -- Antibody GMT testing as above.
- Addition of strains, new subtypes:
  -- Antigen content of old strains must not be decreased.
  -- Immunogenicity testing by horse vaccination/challenge using a field-relevant challenge strain, ≥10 vac + 5 controls.
- Firms are encouraged to develop the SRD assay as a measure of HA antigen content during production. Reagents are available at NIBSC.

Dr. Foley will address this.
• Since 2004, canine influenza has spread to dogs in 25 states & Canada.

• Independently detected in foxhounds in England

• 1% to 8% mortality
Current vaccines

• Merial—Recombitek-Flu (Merial) recently updated with OH/03

• Calvenza (Boehringer-Ingelheim) recently updated with OH/03

• Other vaccines use older strains

• Flu-Avert (Intervet) remains the only MLV

• Japan is reviewing its virus strains
  La Plata/93 (American)
  Avesta/93 (Eurasian)
  Will not allow live virus vaccine at PEQ

• AUS will probably not allow live virus vaccine at PEQ
  NZ will not allow live virus vaccine at PEQ
Any questions?