Vaccination Strategy for Swine & Swine Workers: Swine Influenza Virus, pandemic H1N1, & other Flu Viruses
7th Annual National “One Medicine” Symposium
December 9, 2009

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Safeguarding Animal Health
Influenza Virus

- Subtypes: antigenic drift, shift
  - Random mutations
  - Reassortment

- **Avian** flu viruses prefer HA cell receptors with $\alpha_2$-$3$-linked sialic acid residues;

- **Mammalian** flu viruses prefer HA cell receptors with $\alpha_2$-$6$-linked sialic acid residues

- Swine have both types of cell receptors for HA: dual infection may allow reassortment and development of new subtypes and new variants of subtypes
Animal Flu Vaccines for pigs, poultry, horses, dogs

Not...

or
Swine Influenza Virus

- H1N1 - ‘classical’ (1930), ‘atypical’, ‘variant’
- H3N2 - late 1998 (hu x sw, hu x sw x av)
- H1N2 - 2001; hu-H1 viruses - 2005
- H2N3 - 2006 (av X sw)

- H2 not in humans since 1968 = pandemic risk
- European vs. American strain differences
- Other strains detected in pigs:
  H1N7, H3N1, H4N6, H9N2, HPAI H5N1, H3N8, pH1N1
Current Flu in N. American Swine

- pH1N1 (+ ARG, UK, NOR, HK, AUS, IRE, JAP, etc) and other H1N1: respiratory disease in pigs
- H3N2: abortions, off feed, fever, mortality
- Most H3N2 isolates are triple reassortants with a similar ‘cassette’:
  - Human (HA, NA, PB1)
  - Swine (NS, NP, M)
  - Avian (PB2, PA)
- swH3N2 similar to huH3N2 (vaccines may protect), swH1N1 not similar to huH1N1 (more susceptible)
- H1N1, H3N2, H1N2, H3N1 strains continue to drift & reassort: need surveillance and vaccine changes
Pandemic H1N1 Influenza

- pH1N1 is a quadruple reassortant also with a ‘cassette’ but: Eurasian NA & M genes unique
  - Human (PB1)
  - N. American Swine (HA, NP, NS)
  - Eurasian Swine (NA, M)
  - Avian (PB2, PA)

- Current SIV vaccines may not adequately protect against pH1N1-induced clinical signs + shedding

- Countries had bans on swine or pork product imports from part or all of the US, now ~7 [Pork is safe!]

- **Goal**: prevent spread in the US swine herd, e.g. from exposure to an infected person or animal
Vaccination Strategy

- Vaccinate humans and swine
  - 75,442 US farms w/ swine
  - 30,546 US hog operations
- Vaccines protect best vs. homologous strains
- Antigenic drift and shift require changing antigenic content periodically
- Surveillance, prediction – can be very helpful: 40% vs. 85-95% effective for human flu
- Mechanism to replace/add strains fast is needed

*provided by National Swine Registry*
Current Flu Vaccines for Swine

- Inactivated vaccines: SIV strains alone or with other fractions; no live products

- Commercial vaccines
  - Variety of H1N1 & H3N2 strains from Master Seed Viruses
  - PRV, E rhu, M hyo, Parvo, Lepto 5- or 6-way

- Autogenous vaccines
  - firms produce from original herd isolates

- 9CFR 107.1 VCP exemption to certain requirements
  - pH1N1 subunit
For Standard Full USDA License
Supporting Data Must Demonstrate **Purity** of:

- Master Seed
- Master Cell Stock
- Ingredients
- Completed Product
  - bacterial/fungal contamination
  - inactivation
Supporting Data Must Demonstrate Safety in:

- Laboratory animals
- Host animals
  - Master Seed Testing (live)
    - Reversion to virulence
    - Shed and Spread
    - Environmental safety
  - Efficacy studies (limited numbers)
  - Field safety
    - Normal conditions of use, multiple sites
    - Reaction rates
- Final product (serial release testing)
Supporting Potency and Efficacy Data Must Demonstrate:

- Support of label claims (age, route, etc.)
- Master Seed immunogenicity (usually host animal vaccination/challenge)
- Established completed product potency
- Duration of immunity
- Stability
VS Memo 800.111 on Viral Strain Changes in Inactivated Equine and Swine Influenza Vaccines

• To replace/add strains using this method, no substantial production changes
• Strains can be subtracted or added w/o repeating full-scale efficacy and field safety studies
• Justification of strain replacement/selection is required
• No more than 3 strains of a subtype per licensed product
• H and N subtypes stated
• Dropping of irrelevant strains encouraged
Methods for Using SIV Vaccines

- Standard license per 9CFR requirements
- VS Memo 800.111 for expedited strain changes in already licensed products
- Conditional license
- Autogenous license
- VCP exemption
Conditional License

- Title 9 Code of Federal Regulations (102.6) and VS Memorandum 800.75
- Emergency: emerging disease
- Limited market or local situation
- Other special circumstances
- License expiration
- Special labeling
- Live, killed vaccines
Conditional License

Pros

- Purity, safety, well known
- Master Seed tested
- Reasonable expectation of potency and efficacy
- Wider distribution
- Relatively quick
- Proceed to standard license

Cons

- Time to license
- Efficacy may be uncertain
- May lack potency test for each serial
- Distribution may be limited
- Limited to domestic products (no permits)
Methods for USDA Licensure of Flu Vaccines for Swine

- Standard full license with all testing completed
  - New or unique strains, new production method

- Expedited strain change in inactivated vaccine
  - Vaccine is an already-licensed product
  - Production method is the same

- Conditional license pending efficacy study
  - Where there is reasonable expectation of efficacy

- Autogenous license for inactivated vaccine
  - VCP, herd of origin, adjacent herd restrictions
Autogenous License

- 9 CFR 113.113 and VS Memo 800.69
- Inactivated products only
- Veterinarian (or approved nonvet specialist)-Client-Patient relationship
- Restricted to herd of origin (adjacent premises under certain conditions)
- Restricted to domestic agents
- Licensed facility, approved Outline of Production
# Autogenous License

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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</thead>
<tbody>
<tr>
<td>✪ Basic purity known (freedom from bacteria, fungi)</td>
<td>✪ Not tested for extraneous agents</td>
</tr>
<tr>
<td>✪ Inactivated</td>
<td>✪ Host animal safety, potency and efficacy not established</td>
</tr>
<tr>
<td>✪ Laboratory animal safety known</td>
<td>✪ Limited distribution (primarily herd of origin)</td>
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<tr>
<td>✪ New isolates</td>
<td>✪ No USDA confirmatory testing of seeds</td>
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<tr>
<td>✪ Quick</td>
<td>✪ Limited to domestic agents</td>
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CVB is Providing pH1N1 Master Seed Viruses (MSV) to Firms

- Three tested & approved pH1N1 viruses for use in a conditionally licensed vaccine:
  - A/CA/04/09
  - A/MX/4108/09
  - A/reassortant/NYMC X-179A

- Firms don’t each have to develop their own:
  - Saves the firms’ time: they work on other aspects of licensure
  - Saves CVB time: confirmatory testing done on one set of MSV, not each firm’s MSV
CA/04, MX/4108 H1N1 MSVs

- CDC - NADC - CVB
- 2 passages in Madin Darby Canine Kidney (MDCK)
- Pig passaged at NADC
  - 5-week-old cross-bred pigs
  - Inoculated intra-tracheally
  - 2 mL of $1 \times 10^5$ 50% TCID50
  - Euthanized on 5 dpi
  - 50 ml of Lung lavage
- At CVB passaged in MDCK (1X)
  - DMEM, BSA 0.2%, trypsin (TPCK treated) 2 μg/ml
  - CPE 24-48 hrs, freeze-thaw, centrifuged, filtered 0.45 μm
- Not adapted to eggs
A/reassortant/NYMC X-179A

A/California/07/2009 (H1N1)v

NYMC X-157 (H3N2)

A/New York/55/2004 (H3N2)

A/Puerto Rico/8/1934 (H1N1)
## Propagation of pH1N1 MSV

### 4 Master Seed Viruses

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<thead>
<tr>
<th></th>
<th>A/CA/04/09</th>
<th>A/MX/4108/09</th>
<th>X-179A (with CA/07 HA and N)</th>
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</thead>
<tbody>
<tr>
<td>Pig passage (NADC)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Propagated</td>
<td>MDCK</td>
<td>MDCK</td>
<td>Eggs</td>
</tr>
</tbody>
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**MDCK -grown:**

**Egg –grown:**

![MDCK-grown demonstration](image1.png)

![Egg-grown demonstration](image2.png)
Extraneous Agent Testing - 1
FA on 6 Cell Lines

- Bovine virus diarrhea virus 1 and 2
- Reovirus
- Rabies virus
- Bluetongue virus
- Bovine adenovirus 1 and 5
- Bovine parvovirus
- Bovine respiratory syncytial virus
- Canine coronavirus
- Canine distemper virus
- Canine parvovirus
- Porcine adenovirus
- Porcine parvovirus
- Transmissible gastroenteritis virus
- Porcine hemagglutinating encephalitis virus
- PRRSV
Extraneous Agent Testing - 2

- Testing for hemadsorbing, cytopathogenic, fluorescent antibody staining viruses
- Testing for avian lymphoid leukemia
- Testing for bacteria, fungi, mycoplasma
- PCR assays for reticuloendotheliosis virus, chicken anemia virus, PCV-2, mycoplasma
- RT-PCR assays for PRRSV, Pestivirus
- Pan-human microarray assay
- Mouse safety testing
The “One Medicine” Perspective
Surveillance

- Present for many years: industry, academia
- in 2008, a more integrated approach: SIV Pilot Project developed by CDC-USDA
- With pH1N1, accelerated surveillance for flu in swine
  - Voluntary private vet samples (nasal swabs, lung) from clinically ill animals to the NVSL/NAHLN
  - Samples from clinically ill animals identified at public events or markets
  - Epidemiological follow-ups in swine herds exposed to human patients with ILI
Surveillance Goals

- Detect new influenza strains in swine in a timely manner
- If present, determine distribution and prevalence of the new strains in swine
- Determine genetic characteristics of new viruses necessary for vaccine & diagnostics development
- Develop a National Flu Vaccine Strain Selection System for swine
pH1N1 Staff

Front row:
• Sandy Conrad
• Melisse Schilling
• Mary Beth Evans
• Amy Shaffer
• Pat Foley
• Joe Hermann

Back row:
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• Deb Narwold
• Dani Koski
• Alethea Fry
• Donna Gatewood
• Peg Patterson
• Doug Murtle

Questions or comments???