Vaccine/Vaccination Terminology

- **Efficacy**: vaccine passes a lab challenge test
- **Effectiveness**: vaccine provides protection under field conditions (implies proper application & coverage)
- **Potency**: adequate amount of antigen (HA) to provide a strong immune response in field
  - Direct (Ag [HA] content, e.g. 0.3-7.8 μg or 512 HA units/dose) or indirect assessment (HI titers in immunized poultry, e.g. ≥ 1:32)
  - Determine mean protective dose (PD_{50}); e.g. minimal 50 PD_{50} per dose (50 PD_{50})
- **Surveillance**: looking for H5 virus in field
- **Monitoring**: looking at vaccinated flocks for serotiters indicating protection and coverage
Introduction

- Historically - Broad cross protection within a hemagglutinin subtype; i.e. H5N2, H5N9, etc. protects against H5N1 HPAI viruses (inactivated AI and live recombinant vaccines)
  - Experimental protection studies support the claim
  - Field success in using existing H5 vaccines in H5N1 HPAI control in Asia: e.g. Mexican, USA and European H5 vaccine strains in Asia
Historical H5 Vaccines – Similar antigenicity: wild birds viruses and initial AI outbreak viruses in poultry (Swayne et al., Av Dis 45:355-365, 2001)

As the virus lineage becomes enzootic in gallinaceous poultry, the HA drifts away from root
Homosubtypic HA Protection by AI Vaccines

- Fowl pox with H5 AIV gene insert
- Different challenge viruses (87.3-100\% aa sequence similarity)

* challenge viruses

(Updated from Swayne et al., Vaccine 18:1088-1095. 2000)
Decreasing AIV Susceptibility: Biotechnology to Solve Genetic Drift

Chickens vaccinated SQ 1d with rFP-H5-Ire/83 and IN challenged at 3 wks with $10^{5-6}$ EID$_{50}$ of HPAIV

- Excellent protection from mortality using diverse H5 AIV
- Reduction in virus replication and shedding from respiratory and digestive tracts

<table>
<thead>
<tr>
<th>Challenge Virus</th>
<th>Subtype</th>
<th>HA Similarity to Tk/Ire/83</th>
<th>Mortality (MDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ck/Scotland/59</td>
<td>H5N1</td>
<td>92</td>
<td>0/10</td>
</tr>
<tr>
<td>Tern/S. Afr/61</td>
<td>H5N3</td>
<td>93.1</td>
<td>0/10</td>
</tr>
<tr>
<td>Tk/Ontario/66</td>
<td>H5N9</td>
<td>89.1</td>
<td>0/10</td>
</tr>
<tr>
<td>Ck/PA/83</td>
<td>H5N2</td>
<td>87.3</td>
<td>0/10</td>
</tr>
<tr>
<td>Tk/Ireland/83</td>
<td>H5N8</td>
<td>100</td>
<td>0/10</td>
</tr>
<tr>
<td>Tk/England/91</td>
<td>H5N1</td>
<td>94.2</td>
<td>0/10</td>
</tr>
<tr>
<td>Ck/Queretaro/95</td>
<td>H5N2</td>
<td>89.3</td>
<td>0/10</td>
</tr>
<tr>
<td>HK/156/97</td>
<td>H5N1</td>
<td>90.2</td>
<td>0/10</td>
</tr>
<tr>
<td>Ck/S. Korea/03</td>
<td>H5N1</td>
<td>89.9</td>
<td>0/10</td>
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<tr>
<td>ck/Vietnam/04</td>
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<td>88.4 est</td>
<td>0/22</td>
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<td>WS/Mongolia/05</td>
<td>H5N1</td>
<td>89.7</td>
<td>1/8</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>80-100%</td>
</tr>
</tbody>
</table>

(Swayne et al., Vaccine 18:1088-1095. 2000)
Higher HA identify between vax and challenge AIV

• Respiratory shedding – significant reduction

• Alimentary shedding – no association in reduction

(Swayne et al., Vaccine 18:1088-1095. 2000)
H5 viruses are diverse – N. Amer. and Eurasian lineages

H5N1 HPAI is not a single virus, but a family of viruses with 10 lineages and many sublineages

Virus is drifting as other influenza A viruses have done – from natural infections and “vaccine pressure”
Antigenic Diversity of H5N1 Avian Influenza Virus: AgC-H5 (Ferret Serum)

Source: Ron Fouchier
Antigenic Diversity of H5N1 Avian Influenza Virus: AgC-H5 (Chicken Serum)

Source: Erica Spackman
Impact of Drift on Protection

Antigenic Cartography

- Historical H5 Vaccines – Similar antigenicity
- Drifting of HA away from root

  - Good protection: Ck/HK/220/97, Ck/Legok/03, VN/1203/04, Ck/WJ/HAMD/06
  - Intermediate protection: Ck/Papua/06
  - Poor protection: PWT/06
Other Examples of Antigenic Drift


• China (2004-) (Chen et al., OIE Rev Sci Tech 28:267-274, 2009):
  – Re-5 (rgA/dk/Anhui/1/2006 [H5N1](2.3.4): 2008-12

Antigenic drift must be continually addressed & vaccine seed strains updated; future will require reverse genetic LPAI seed strains based on hemagglutinin of recent field HPAIV

How do you update?

Ongoing and adequate surveillance and monitoring in vaccinated and non-vaccinated populations

- Passive surveillance for mortality events in all vaccinated flocks and subset of non-vaccinated flocks – VI and sequencing of isolates
- Active surveillance in subset of vaccinated flocks with normal mortality profile – VI on deads as routine with sequencing of isolates
- Ongoing genetic analysis of all H5 viruses (phylogeny)
- Subset of genetically diverse isolates are HI tested & analyzed for antigenic divergence (cartography)
- Challenge testing of subset of antigenic divergent viruses
- Proposed seed strain change based on frequency of antigenic variant viruses in field
Global marketing of a single H5 vaccine seed strain does not always meet the local (national/regional) needs for efficacy; i.e. science and not marketing should prevail

Solutions:

- **Best:** Updating vaccine seed strains to match antigenic drift in field viruses (reverse genetic seeds to match field virus)
- **Adjunct:** Increase antigen mass in inactivated vaccine – HA protein quantity (HA units or 50 PD$_{50}$) (Source: CLEVB Egypt, challenge tests for vaccine batch release)
- **Adjunct:** Multiple vaccinations to enhance immunity in field – use of heterologous H5 vaccine seeds (bivalent or multiple heterogenous monovalent)
  - Prime-Boost usage
  - More use of live recombinants in hatchery
- **Adjunct:** Adjuvants to enhance immune response (current [proprietary] & future [oils, surfactants & cytokines])
Increasing Antigen Content


- HI serology titers of GMT ≥ 8 (Swayne et al., Av Pathol 28:245-255, 1999) or ≥10 (Kumar et al., Av Dis 51:481-483, 2007) were associated with survival when had antigenically similar seed and challenge viruses

- HI serology titers of GMT ≥ 40 (Kumar et al., Av Dis 51:481-483, 2007) were associated with prevention of challenge virus shedding from the oropharynx in the majority of vaccinated chickens and GMT ≥ 128 (Swayne, et al., Av Path 35:141-146, 2006) were associated with preventing challenge virus shedding from the oropharynx in all vaccinated chickens

- **Newer Data:** HI serology titers (challenge virus antigen) of GMT ≥ 32 associated with survival and GMT ≥ 64 associated with preventing respiratory replication
Increasing Antigen Content

Proposed National Minimum Standard: GMT $\geq 120$

(128) HI titer as optimal (using vaccine seed as HI test antigen)

If HI test using challenge or antigenic drift variants produce mean titers of GMT $\leq 32$, vaccine seed change should be further examined

- Challenge studies to assess protection
- Examine other field viruses in HI tests to determine how common the antigenic variant viruses are in the field
Other Related Issues

Pre-develop logistics for vaccination and exercise vaccination plan for emergency or ‘routine’ usage

Vaccine availability: commercially or vaccine bank within the country

- Completed vaccine licensing/registration process, or have emergency authority
- Stockpiles available in country through manufacturing capacity or importation to meet need

License issues:

- Specific seed strain for each license submission
- Replacing seed strain requires additional data and varies with each country: safety to full efficacy and potency
  - Cassette concept – seed strain replacement with safety and seropotency data
Conclusions

• Genetic and antigenic variant HPAI/LPAI field viruses, resistant to licensed H5 AI vaccines, have been identified in Mexico, Indonesia, Egypt, Vietnam, Hong Kong and China

• Updating vaccine seed strains is needed to assure the most efficacious and effective vaccines are used in the field

• More rg inactivated seed strains and recombinant vaccines will be needed for antigenic matching

• Need more rapid means of licensing updates in vaccine seed strains through national regulatory processes
Conclusions

- Increasing antigen content in vaccines, using multi-vaccinations with antigenically diverse seeds, or single vaccination with bivalent vaccines (with antigenically diverse seeds) can compensate for some antigenic diversity of field viruses, but will not replace the periodic need to update seed strains.
- Need to update the minimum potency of all H5 and H7 AI vaccines.
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