Update on Zoonotic Infections with Variant Influenza A Viruses in the USA

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OFFLU Swine Influenza Virus Surveillance Network

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Reporting Requirements for Novel Influenza A Infections in Humans

- In 2007, novel influenza A infections nationally reportable to the National Notifiable Diseases Surveillance System

- Novel influenza A viruses = those that are different from currently circulating human H1 and H3 viruses

- Includes those that cannot be subtyped using standard methods and reagents
Inter-Agency Agreement between CDC and USDA

Collaboration between the Influenza Division and USDA, Animal and Plant Health Inspection Service (APHIS)
National Veterinary Services Laboratory (NVSL).
Development of a National Swine Influenza Virus (SIV) Surveillance Program

Rapidly detect changes in swine influenza virus to increase the knowledge of the Impact of SIV changes on swine health
- Risk assessment
  - identify swine influenza viruses that may pose a threat to human health (ie H2N3, H3N1)
  - co-ordination of surveillance during human outbreaks
- develop improved human biosafety practices to minimize transmission
- Share viruses/reagents

Use of viruses/data from swine influenza surveillance
- Mouse and ferret pathotyping
- Flu diagnostic assays
- Antiviral resistance testing
- Antigenic comparisons
- Pre-pandemic Vaccine Development
- Human population immunity

Provide diagnostic, epidemiologic, and experimental data regarding SIV infection to swine stakeholders
develop new diagnostic reagents for swine
provide material for vaccine updates
improve biosecurity practices to minimize transmission.
Evaluate mutations and how they affect flu diagnostic assays

Current FDA approved CDC Flu rRT-PCR Dx Panel rely on real-time RT-PCR primers and probes to the following gene targets

- Influenza A - M gene
- Influenza B – NS gene
- Human H3 – HA
- Human H1pdm – HA
- Influenza A/pdm09 – NP gene

RUO - swH3 – HA
RUO – swH1 – HA

Testing Algorithms with the current CDC Flu rRT-PCR Dx Panel identifies H3v and H1v human influenza infections.

Surveillance for mutations in the primer and probe regions must be continually monitored
Antiviral Susceptibility of variant viruses

- All H3N2v and H1N1v viruses evaluated are resistant to the amantadine class of drugs (amantadine, rimantadine).

- CDC has deployed antiviral susceptibility testing at several public health departments and at CDC labs.

- The pyrosequencing test used for human H3N2 and H1N1 viruses is suitable for testing variant viruses as well.

- All H3N2v and H1N1v viruses evaluated so far appear to be susceptible to the commercially available neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®).
Antigenic comparisons against current human prototype variant vaccines

- All H3N2v viruses tested are antigenically similar to the H3N2v candidate vaccine A/Minnesota/11/2010 but antigenically distinct from seasonal H3N2 viruses. Antigenic differences in H3N2v must be continually monitored for vaccine match.
Summary of Swine Influenza virus circulation in pigs and detection of human infections

1918 - First swine H1N1 isolate 1930
1930 - swH1N1 in Fort Dix, NJ
1976 - 1990-1995 at least 9 rH1N1 human infections detected
1997-1998 - First rH3N2 detected in swine
1998 - trH1N1 first detected in human in 1998
2005 - rH1N1, rH1N2, rH3N1, rH2N3 also detected in swine
2009 - 2009 pandemic influenza
2011 - 15 cases since July 2011
13 cases H3N2v
1 case H1N1v
1 case H1N2v

Classical Swine - North American Lineage
North American Avian Lineage
Seasonal H3N2
Eurasian Swine Lineage
H3N2v 2014

Total H3v cases: 3

- 1 case in [Violet]
- 2 cases in [Light Blue]
Influenza A(H3N2)v activity in 2015

Two cases of A(H3N2)v were identified in the United States

- Direct swine contact was reported in both instances.

- One patient from Michigan developed illness in June and recovered following oseltamivir treatment.

- In July, an immunocompromised person from Minnesota developed an acute respiratory illness and tested positive for A(H3N2)v.

- Virus isolates from each patient belonged to separate phylogenetic groups of the A(H3N2)v haemagglutinin tree.
Genome Comparisons of H3N2v 2005-2015

- Classical Swine – North American lineage
- Avian – North American lineage
- Seasonal H3N2
- Eurasian swine lineage (from H1N1 pdm09 virus)
- Gene derived from H1N1 pdm09 virus

2005-2010

Majority of 2011-2012 (n>300) and 2013 from Indiana (n=13)

2013 (n=5)
Ohio, Illinois, Indiana, Michigan

2014 (n=3)
Ohio, Wisconsin

2013 (n=1)
Iowa

A/Minnesota/38/2015
A/Michigan/39/2015
Evolutionary Relationships Among Influenza A Variant (H3N2) HA, 2015
### Status of A(H3N2)v candidate vaccine virus development

<table>
<thead>
<tr>
<th>Candidate vaccine viruses</th>
<th>Type</th>
<th>Institution</th>
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<tbody>
<tr>
<td>A/Minnesota/11/2010 (NYMC X-203)</td>
<td>Conventional reassortant</td>
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<tr>
<td>A/Indiana/10/2011 (NYMC X-213)</td>
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### HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA H3N2v VIRUSES

<table>
<thead>
<tr>
<th>REFERENCE ANTIGENS</th>
<th>Group</th>
<th>KS/13</th>
<th>IN/10</th>
<th>MN/11</th>
<th>MN/11 X-203</th>
<th>WI/24</th>
<th>HI/03</th>
<th>OH/13</th>
<th>IN/21</th>
<th>OH/4319</th>
<th>OH/2</th>
<th>SWITZ</th>
<th>3C.3a</th>
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<th>Human Pool - 2013/14 vaccinees*</th>
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**TEST ANTIGENS**

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Indicates comparison to candidate vaccine virus

* Post-vaccine immune serum pool from adult (19-49 yrs) vaccinees
Influenza A(H1N1)v and A(H1N2)v activity in 2015

Two cases of A(H1N1)v were identified in the United States

- A fatal case was detected in Ohio during April in a person with potential occupational exposure to swine.

- Second severe case in Iowa was hospitalized in August. Direct contact with swine was reported.

- The HA genes of both viruses belonged to the classical swine gamma lineage but were genetically distant to the A(H1N1)pdm09 vaccine virus, A/California/7/2009
Genome Comparisons of H1N1v Viruses

Classical Swine H1N1 – North American Lineage
Avian – North American Lineage
Seasonal H3N2
Eurasian Swine Lineage
Gene derived from H1N1 pdm09 virus

A/Missouri/12/2012 H1N1v

A/Arkansas/14/2013 H1N1v

A/Minnesota/33/2014 H1N1v

2009 Pandemic H1N1

A/Iowa/39/2015 H1N1v

A/Ohio/09/2015 H1N1v
**HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA A(H1N1)v**

**REFERENCE ANTISERA**

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<tr>
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<th>IA/1</th>
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<th>Human pool - 2013/14 vaccinees *</th>
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</table>

**TEST ANTIGEN**

| 7 A/IOWA/39/2015 | H1N1v (gamma) | 160 | 80 | 80 | 40 | 1280 | 640 | 320 |

Indicates comparison to CVV

* Post-vaccine immune serum pool from adult (19-49 yrs) vaccinees
Compared to A/California/07/2009 there were 46 amino acid changes in the HA protein.

Genetic analysis of the hemagglutinin gene of the H1N1v virus detected the presence of a D222G amino acid change in the receptor binding site (D225G in H3 numbering).

Substitutions at this position (D222N or G) have been detected occasionally in H1N1 viruses isolated directly from swine, particularly in viruses of the H1N1pdm09 lineage.

In humans, the D222G substitution has been detected in viruses from severe and fatal cases of A(H1N1)pdm09 infection, although D222G has also been found in humans with mild disease.

- This substitution may occur during the course of infection in humans or during serial passage in laboratory host systems.
- In humans, this substitution is detected more often in A(H1N1)pdm09 viruses isolated from the lower respiratory tract, which is a site more likely to be sampled in severe/fatal cases. This H1N1v virus was sampled from the lower respiratory tract.

While the D222G substitution can be associated with more severe disease, its public health significance remains unclear.

Genetic analysis of the hemagglutinin gene of this H1N1v virus also identified a substitution at position 155 (G155E) within immunodominant antigenic site B.

- Serologic studies have indicated that human A(H1N1)pdm09 viruses with this change show reduced binding to immune sera raised to the vaccine virus A/California/07/2009.
- Mutations at this position have been detected in H1N1 viruses isolated from swine.
312 US sequences with 155E
Ongoing studies

Generation of Ohio/9 CVV
  - ferret antisera production/antigenic characterization

Generation of Ohio/9 CVV without 155E
  - ferret antisera production/antigenic characterization

Pathotyping in ferrets
  - Ohio/9 vs. related H1v viruses (without 155 or 222 subst.)

Vaccine efficacy in ferret model vaccinated with current seasonal vaccine
  - challenge ferrets with Ohio/9 wt
Acknowledgements

USDA
- Sabrina Swenson
- Amy Vincent

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- National Influenza Centers

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- Rebecca Garten
- Ruben Donis
- Sue Trock