The Mother of All Pandemics

100 Year Anniversary of the 1918 H1N1 Pandemic

A lasting impact on U.S. swine

Amy L. Vincent, DVM, PhD
Research Veterinary Medical Officer
National Animal Disease Center
USDA-ARS Ames, IA
Presentation Overview

• 1918 Spanish Flu – the “Mother of all Pandemics”
• Influenza ecology
• Evolution of IAV in swine
• Current genetic diversity of IAV in US/North America
• Antigenic consequence of IAV diversity
• Human-swine interface
• Why does a century old pandemic matter?
Mother of all pandemics?

Reassortment History of Pandemics & US Swine

1918 Spanish
1957 Asian
1968 Hong Kong
1977 Russian
2009 H1N1pdm09

H1N1 1918 Spanish
H2N2 1957 Asian
H3N2 1968 Hong Kong
H1N1 1977 Russian
H1N1 2009 H1N1pdm09

H1N1 classical
H1N2 Eurasian avian
1998 Triple Reassortant
H3N2 Delta Reassortant

H1N1 2009 H1N1pdm09
H3N2 PDM Reassortant

H1N1 PDM Reassortant
H1N2 PDM Reassortant
1918-19 - Three Waves

• 1st Wave - Late 1917, mostly early 1918.
  • A few sporadic reports, appeared to be milder

• March 1918 - Fort Riley, Kansas.
  • Spread among military camps and among troops in World War I

• By fall 1918 into winter 1919, the disease began sickening civilians in most U.S. cities and towns.
  • 2nd Wave was the most devastating.
    • Patriotic marches and military recruiting events
    • Some cities began banning all public gatherings

• Resolution by Congress for $1,000,000 to fight flu.
  • Doctors and scientists thought cause was a bacteria and tried making bacterins as vaccines.

• Heavy toll on troops in Europe, so more troops sent by ship.
  • Ideal situation to amplify and spread flu.

• September 1918 reached the peak of the outbreak & mortalities.

• In November, Germany surrendered and troops were back on ships to return home, Armistice Day celebrations, etc., so the spread continued.

• A milder 3rd wave occurred in early 1919.
1918 H1N1 – the toll

• Overall estimates up to 1/5 of the world’s population at the time were infected
• Between 20-50 million deaths (some estimates up to 100 million)
  • 18 million killed in WWI

Different stages of skin coloration as seen during the 1918 influenza pandemic characterized as “heliotrope” or deep blue cyanosis. Reproduced with permission from the Lancet archives.

Shanks, D. Travel Medicine and Infectious Disease 2015 13, 217-222DOI: (10.1016/j.tmaid.2015.05.001)
Presentation of severe 1918 cases

• Clinical presentation in severe cases:
  • Epistaxis
  • Cyanosis followed by rapid deterioration and death

• Severe histopathology described
  • Pulmonary hemorrhage and edema
  • Epithelial necrosis
  • Vascular necrosis

• Severe necrotizing hemorrhagic bronchopneumonia with or without evidence of bacteria

• Acute respiratory distress syndrome (ARDS)-like lesions
  • Alveolar edema and hemorrhage

What made 1918 H1N1 so pathogenic?

• The reasons for the severity of 1918 H1N1 remains a mystery
  • “W-Shaped” Mortality Curve
  • Unique virulence
    • Reconstructed 1918 H1N1 viruses not overly revealing in experimental challenges
• Different variants of H1N1 circulating
• Additional pathogens – secondary bacteria
• Global migration (war) and harsh conditions

• Antigenic sin or antigenic imprinting

Influenza in humans prior to 1918

Historical evidence for prior pandemics
- 1830s H1N1
- 1850s H1N8
- 1890s H3N8
- 1900s H1N8: This H1 diverged to modern classical swine and human seasonal (pre-2009)
VAERD
Vaccine-Associated Enhanced Respiratory Disease

- Mismatched challenge to whole inactivated virus vaccine
  - Same subtype, but antigenically mismatched
  - H1 and H3 models
- Whole Inactivated Virus (WIV) + Oil-in-Water Emulsion Adjuvant
  - Other adjuvants did not induce VAERD
- Mismatched passive antibodies from vaccinated dams
- HA subunit protein with adjuvant
- Microscopic lesions:
  - Interlobular edema
  - Alveolar edema & hemorrhage
  - Interstitial pneumonia
  - Peribronchiolar lymphocytic cuffing
  - Suppurative bronchitis/alveolitis
  - Lymphocytic subepithelial infiltration

- WIV induces cross-reacting whole-virus antibodies that do not cross-react by HI or SN.

Vincent, Gauger, Rajao, et al, various publications since 2008
Can the sequence of exposures misdirect the immune response and recapitulate the enhanced lung pathology previously only seen with WIV in our VAERD models?
**Study Design**

- Weaned pigs 3wk-old acclimate 1 week
- VACCINATION/EXPOSURE 1
- BLOOD COLLECTION (-49 dpi)
- BLOOD COLLECTION (-21 dpi)
- CHALLENGE
- NECROPSY
- EUTHANASIA

### Table of Group Exposures and Challenges

<table>
<thead>
<tr>
<th>Group</th>
<th>Exposure 1</th>
<th>Exposure 2</th>
<th>Challenge</th>
<th>Nec1</th>
<th>Nec2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>rgH3N2</td>
<td>None</td>
<td>rg(2+6)pH1N1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>rgH3N2</td>
<td>rg(1+7)ΔH1N2</td>
<td>rg(2+6)pH1N1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>rg(1+7)ΔH1N2</td>
<td>rg(2+6)pH1N1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>None</td>
<td>rg(2+6)pH1N1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>WIV rg(1+7)ΔH1N2</td>
<td>WIV rg(1+7)ΔH1N2</td>
<td>rg(2+6)pH1N1</td>
<td>10</td>
<td>-</td>
</tr>
</tbody>
</table>

**Notes:**
- dpi = days post infection
- dpi = days post infection
- VACCINATION / EXPOSURE 1
- BLOOD COLLECTION (-49 dpi)
- BLOOD COLLECTION (-21 dpi)
- BLOOD COLLECTION (-63 dpi)
- BLOOD COLLECTION (-84 dpi)
- EUTHANASIA
- CHALLENGE
- NECROPSY
- VACCINATION / EXPOSURE 2
- BLOOD COLLECTION (14 dpi)
Exposure 1
- none
- rgH3N2
- rgH3N2
- none
- WIV

Exposure 2
- none
- none
- rg(1+7)H1N2
- rg(1+7)H1N2
- none
- WIV

Challenge
- none
- rg(2+6)pH1N1
- rg(2+6)pH1N1
- rg(2+6)pH1N1
- rg(2+6)pH1N1
- WIV

Macroscopic and microscopic Pneumonia Lesions

Microscopic lesion score
- Microscopic lung score (0-22)

Percentage of Lesions
- Macroscopic %
- Microscopic % 0-22
Modern History of Flu

- 1931 IAV first isolated from pigs
- 1933 IAV first isolated from humans
- 1935 first influenza vaccine
- 1952 WHO began global surveillance network
- 1956 CDC became WHO collaborating center
- 1957 H2N2 Asian flu pandemic
- 1968 H3N2 Hong Kong flu pandemic
- 1973 WHO selects first vaccine strain
- 1976 Fort Dix “swine flu” scare
- 1977 H1N1 Russian flu re-emerges
- 1986 First WHO vaccine strain composition meeting
- 1997 First H5N1 AIV outbreak in humans
- 2006 First Pre-pandemic (animal) candidate vaccine strain
- 2009 H1N1pdm09 pandemic from swine lineages
- 2013 First H7N9 AIV outbreak in humans
Today – Seasonal Influenza in Humans

- The 1918 Spanish flu pandemic led to strengthening of national and global public health organizations.
- US DHHS dedicates a major portion of its budget to influenza (NIH, FDA & CDC).
- CDC began in 1942, established an influenza unit in 1957.
  - ~200,000 Americans hospitalized for ILI each year
  - Annual deaths range in the 10,000s in the USA
    - Greater toll in developing countries
  - Very young, very old, pregnant, immunocompromised, or pre-existing medical conditions at higher risk
  - CDC major contributor to WHO global influenza program

https://www.cdc.gov/flu/about/disease/2015-16.htm#table2
Influenza ecology & evolution

100 years, why is influenza A virus still a problem?
Clinical Disease
influenza in swine

• High morbidity, low mortality
• All ages affected, typically more severe in younger growing pigs
• Infection limited to respiratory tract
  • Cough, dyspnea, fever, nasal discharge, inappetence
• Self-limiting in most uncomplicated cases
• Predisposes to secondary bacterial infections and is a component of porcine respiratory disease complex
Influenza A Virus

- Orthomyxovirus
- Negative strand RNA genome
- **Segmented genome**
  - 8 segments
  - Encodes 10 (12) proteins
- Enveloped
- **2 major surface glycoproteins**
  - Hemagglutinin (HA) – 18 subtypes
    - Receptor binding site
  - Neuraminidase (NA) – 11 subtypes
    - Enzyme to release budding progeny virions

[Source](http://web.uct.ac.za/depts/mmi/stannard/fluivirus.html)

IAV evolves by 2 main processes:
- Genetic mutation
- Reassortment

IAV escapes population immunity by:
- Antigenic drift
- Antigenic shift
Pigs are a natural host for IAV
Diversity of swine IAV shaped by human IAV


T.K. Anderson
Timeline of IAV introductions in swine

- 1918 (Spanish Pandemic)
- 1960s (European human H3)
- 1970s (European human H1)
- 1980s (US human H3 TRIG)
- 1990s (US human H1)
- 2000s (2009 H1N1)
- 2010s (US human H3)

- H3N2
- H1N1
- H1N1/N2
- H3N2-TRIG
- H1N1-avian
Countries with H1N1pdm09 in pigs

Nelson and Vincent, Trends Microbiol. 2015
Continued transmission of H1N1pdm09 from humans to pigs
Production practices & the impact on Influenza in swine
Typical pig flow in a commercial farm
All in, All out by farrowing room – piglets weaned offsite

This farm structure represents ~70% of the total industry or about 4.2 million sows
Breeding stock multiplication is represented in this structure and sow numbers
IAV moves with pig flows
IAV moves regionally with pig transport
imported into Iowa annually, along with the ~20 million that are born in Iowa. These are both weaned pigs and feeder pigs. Other corn belt states also receive pigs from within the U.S. and Canada, but Iowa is the pig import mecca. Some sites comingle sources.

Thanks, Canada!
Surveillance for IAV in swine
How do we know what IAV are predominant in the U.S. swine population?

- USDA Surveillance System active since 2009
- Virus isolates have HA and NA sequenced for all, WGS for subset
- Sequences in GenBank
  - A/swine/Arkansas/A01840698/2015
- Isolates available through USDA NVSL repository
  - Email your request to: NVSL_Userfee@aphis.usda.gov
USDA IAV Surveillance
National Animal Health Laboratory Network

Started in 2009

Genetic Diversity of Swine H1 and H3 HA Genes

Jennifer Chang
### HA and NA Clade Combinations

**Rolling 2 year window**

Percentage of HA and NA combinations - Jan 2016 to Dec 2017

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H3.IV-E</td>
<td>0</td>
<td>0</td>
<td>0.18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>H3.IV-B</td>
<td>0</td>
<td>0</td>
<td>0.12</td>
<td>2.02</td>
<td>0</td>
</tr>
<tr>
<td>H3.IV-A</td>
<td>0</td>
<td>0</td>
<td>5.46</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>H3.IV</td>
<td>0</td>
<td>0</td>
<td>0.49</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>H3.Human-like_2016</td>
<td>0</td>
<td>0</td>
<td>0.37</td>
<td>0</td>
<td>0.37</td>
</tr>
<tr>
<td>H3.Human-like_2010</td>
<td>0.37</td>
<td>0</td>
<td>0.06</td>
<td>13.93</td>
<td>0</td>
</tr>
<tr>
<td>H1.pandemic</td>
<td>0</td>
<td>5.21</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H1.gamma2</td>
<td>0.06</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H1.gamma</td>
<td>0</td>
<td>0</td>
<td>10.37</td>
<td>0.31</td>
<td>0</td>
</tr>
<tr>
<td>H1.delt2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H1.delta1b</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>6.26</td>
<td>0</td>
</tr>
<tr>
<td>H1.delta1a</td>
<td>0.06</td>
<td>0</td>
<td>0.12</td>
<td>16.81</td>
<td>0</td>
</tr>
<tr>
<td>H1.beta</td>
<td>0.43</td>
<td>0</td>
<td>0</td>
<td>0.37</td>
<td>0</td>
</tr>
<tr>
<td>H1.alpha</td>
<td>0</td>
<td>0.06</td>
<td>0</td>
<td>6.13</td>
<td>0</td>
</tr>
</tbody>
</table>

**FY18 Quarter 1**

Percentage of HA and NA combinations by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Region1</th>
<th>Region2</th>
<th>Region3</th>
<th>Region4</th>
<th>Region5</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3.IV-B</td>
<td>3.7</td>
<td>3.7</td>
<td>4.55</td>
<td>4.55</td>
<td>22.73</td>
</tr>
<tr>
<td>H3.IV-A</td>
<td>3.7</td>
<td>2.16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H3.Human-like_2016</td>
<td>18.32</td>
<td>16.00</td>
<td>18.02</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>H3.Human-like_2010</td>
<td>0.32</td>
<td>4.86</td>
<td>0</td>
<td>4.55</td>
<td>0.99</td>
</tr>
<tr>
<td>H1.pandemic</td>
<td>0</td>
<td>0</td>
<td>4.55</td>
<td>4.55</td>
<td>0.09</td>
</tr>
<tr>
<td>H1.gamma2</td>
<td>0</td>
<td>14.81</td>
<td>0.54</td>
<td>5.95</td>
<td>0</td>
</tr>
<tr>
<td>H1.gamma</td>
<td>0.04</td>
<td>4.32</td>
<td>0</td>
<td>3.78</td>
<td>14.56</td>
</tr>
<tr>
<td>H1.delta2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H1.delta1b</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H1.delta1a</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total HA & NA combinations**

- Rolling 2 year window: 1630
- FY18 Quarter 1: 159

*Jennifer Chang*
Genotype patterns

H1N1 and H1N2

H3N2

Gao et al., JGV 2017

Rajao et al., JVI 2017
Swine IAV web-based tools

Influenza.cvm.iastate.edu
Michael Zeller

Fludb.org
Tavis Anderson
Antigenic Diversity of IAV in Swine

- Monovalent swine antisera
- Pairwise hemagglutination inhibition (HI) assays
- Collaboration with Nicola Lewis @ University of Cambridge
Cluster-IV H3 IAV in swine at the antigenic level

Strains characterized in the lab (cross-HI's with a established, representative panel)

Inferred antigenic phenotypes over time

<table>
<thead>
<tr>
<th>Year</th>
<th>(n=222)</th>
<th>(n=202)</th>
<th>(n=255)</th>
<th>(n=215)</th>
<th>(n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2015</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2016</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Lewis et al. J. Virol 2014
Unpublished data, M. Bolton & E. Abente
Antigenic diversity of swine H1

Potential antigenic sites in Delta lineage H1

Rajao et al., Virol 2018
N2 mapping by NI – H9N2 antigens

Antigen Colors
- Blue: 1998
- Red: 2002

Sera Colors
- Green: Human sera
- Pale orange: 02A lineage sera
- Purple: 02B lineage sera
- Blue: 98 lineage sera

Bryan Kaplan
with Daniel Perez & Jeff Santos @ UGA
Integrating and synthesizing surveillance data for interspecies transmission to and from humans: 

*a pig tale*
Variant IAV

• When a swine-lineage IAV is detected in humans, it is called “variant” to distinguish it from human seasonal and avian lineages (e.g. H3N2v).

• Non-seasonal detections became reportable to WHO in 2005.

• Since 2005, the CDC developed PCR tests implemented in public health labs to differentiate variant IAV from seasonal IAV and created a Zoonotic Virus Team.
  • 468 total variant detections of all subtypes
  • 309 variants were H3N2v detected in 2012

• Variants tend to be dead end with limited human to human transmission.

• CDC routinely checks cross-reactivity of variants against ferret anti-sera to seasonal vaccine strains and human population sera.
  • Children born after 2001 have limited immunity to H3N2v.

• The CDC presents this data at the WHO vaccine consultation meetings.
  • ~8 variants from the US selected as pandemic preparedness candidate vaccine viruses (along with Eurasian swine H1N1 and several avian influenza strains).
The Fair Connection

TAKE ACTION to Prevent the Spread of Flu Between Pigs and People

Background

Pigs can be infected with their own influenza viruses (called swine influenza) that are usually different from human flu viruses. While rare, influenza can spread from pigs to people and from people to pigs. When people get swine flu viruses, it’s usually after contact with pigs. This has happened in different settings, including fairs. The Centers for Disease Control and Prevention (CDC) recommends people take the following actions to help prevent the spread of flu between pigs and people.

CDC Recommendations for People with High Risk Factors:

• Since 2011, the majority of human variant cases have been associated with agricultural exhibits (county and state fairs).
• The IAV detected in show pigs are similar to those found in USDA surveillance.
• Outbreaks in show pigs tend to coincide with influenza-like illness in the stockman (adolescents and teens) or attendees.
Swine RISK Assessment Pipeline

- What about swine IAV not yet detected in variant cases?
- Is antigenic distance of swine IAV to human seasonal strains an indicator of population immunity?
- Does swine sera reflect ferret anti-sera? Which one is “right?”

Collaboration with Nicola Lewis
And inter-CEIRS collaborators
Swine-human antigenic analysis

Key:
Alpha
Beta
Gamma (large sphere = A(H1N1/swine/Minnesota/A01567490/2014)
PDM (Grey = A/California/04/2009)
Small yellow = delta lineage (Grey=A/Michigan/02/2003)
Pink = 2015 gamma lineage in pigs
Black = A/Ohio9/2015
Scale bar = 1AU or a two-fold difference in HI assay titre

<table>
<thead>
<tr>
<th>Virus 1</th>
<th>Virus 2</th>
<th>AU Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG</td>
<td>A(H1N1)/SWINE/NORTH CAROLINA/A02076926/2015 MDCK2-AG</td>
<td>3.4</td>
</tr>
<tr>
<td>A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG</td>
<td>A(H1N1)/SWINE/NORTH CAROLINA/A01841602/2015 MDCK2-AG</td>
<td>4.9</td>
</tr>
<tr>
<td>A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG</td>
<td>A(H1N1)/SWINE/OHIO/A01847657/2015 MDCK2-AG</td>
<td>5.1</td>
</tr>
<tr>
<td>A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG</td>
<td>A/Ohio/9/2015 MDCK2-AG</td>
<td>4.7</td>
</tr>
<tr>
<td>A(H1N1)/MEXICO/4108/2009 MDCK3-AG</td>
<td>A(H1N1)/SWINE/NORTH CAROLINA/A02076926/2015 MDCK2-AG</td>
<td>3.3</td>
</tr>
<tr>
<td>A(H1N1)/MEXICO/4108/2009 MDCK3-AG</td>
<td>A(H1N1)/SWINE/NORTH CAROLINA/A01841602/2015 MDCK2-AG</td>
<td>4.9</td>
</tr>
<tr>
<td>A(H1N1)/MEXICO/4108/2009 MDCK3-AG</td>
<td>A(H1N1)/SWINE/OHIO/A01847657/2015 MDCK2-AG</td>
<td>5.2</td>
</tr>
<tr>
<td>A(H1N1)/MEXICO/4108/2009 MDCK3-AG</td>
<td>A/Ohio/9/2015 MDCK2-AG</td>
<td>4.4</td>
</tr>
</tbody>
</table>

2015 swine gamma similar to A/Ohio/9/2015 (155E, 169R, 222G)
- A/swine/North_Carolina/A02076926/2015 H1N1-gamma (155G, 169K, 222D)
- A/swine/North_Carolina/A01841602/2015 H1N1-gamma (155E, 169K, 222D)
- A/swine/Ohio/A01847657/2015 H1N1-gamma (155E, 169R, 222D)
Human seasonal H3N2 introduction into swine

The 3rd genotype of human-like H3N2 has been the predominant H3 detected in the USDA swine surveillance system since 2014.

This genotype also infected 16 humans in close contact with swine at fair exhibits in the summer of 2016.
Genetic and antigenic evolution of the 2010 hu-like H3N2 in swine 2017

• Generation 3.1
  • Switched N2 clade from N2-02A to N2-02B.
  • Amino acid changes in HA, position 145 previously shown to be a dominant antigenic site (K145N).
  • Genome constellation: TTTTPT
    • PB2, PB1, PA, NP, & NS from North American swine TRIG lineage
    • M from H1N1pdm09 lineage
  • 62 human variant cases in 2017, nearly identical viruses.
    • Mostly county fairs in Ohio, Michigan, and Maryland + others
    • Iowa case in a swine farm worker
Antigenic drift of 2017 H3N2 K145N in swine

Michael Zeller

Carine Souza
IAV at Human-Swine Interface

- Human seasonal IAV incursion has a major impact on the overall diversity of swine IAV since 1918.
  - The 2010 H3N2 and the repeated H1N1pdm09 incursions are prime examples and have had dramatic impacts in recent years.
  - Once adapted to swine, these viruses can then pose zoonotic risk to humans (variants).
- Once in swine, the genes derived from the 2010-11 human seasonal H3 underwent rapid evolution, combined with multiple reassortment events.
  - The earliest HA genes detected in swine had 18-25 amino acid changes from closest human H3 precursor.
  - Reassortment occurred before widespread expansion.
    - Currently, hu-H3/N2-02B+TTTTPT is most common (genotype 3.1).
      - Associated with swine and human outbreaks.
      - Impact on vaccine strain selection.
- Another H3N2 incursion detected in 2017 in the U.S. from 2016-17 human season and others detected globally.
  - 2017-18 was another H3N2 dominant human flu season – more incursions?!
INFLUENZA CONTROL is not so simple…
Especially if you are a pig.

• Interspecies transmission between humans and pigs continues to occur.
• Human IAV dramatically impacts the genetic expansion of IAV in swine, particularly the H1N1pdm09.
• Vaccines against influenza constantly need updating and not as easy as it seems to make a good vaccine.
• Pig movement adds to the complexity of IAV in swine.

• What have we gained since the 1918 Spanish Flu Pandemic?
Pandemic preparedness by WHO & CDC

- CDC Zoonotic Virus Team dedicated to this area of IAV and working groups with USDA, state animal health, and public health, and many international partners.
- Diagnostic assays at public health labs to detect non-seasonal IAV in human specimen.
- Awareness of influenza like illness off-season and associated with swine contact by physicians and local health departments.
- Sequence and antigenic analysis of animal IAV provides baseline knowledge needed for public health.
  - HI tests with monovalent ferret anti-sera and human population sera for novel IAV detections in humans.
- Moving beyond the simple focus of HA in inactivated vaccines and pairwise HI assays for human vaccine concepts.
  - Prior exposure history, repeated vaccination, NA and other viral targets...
- Vaccine seed strains made and held in reserve.
  - Not just swine, but avian, canine, equine...
Future Opportunities in Swine IAV

• Surveillance data revealing patterns from which to draw vaccine strain decisions for swine and to inform public health.

• Changes in USA vaccine licensing regulations.

• New vaccine platforms and technology – RNA RP vector & LAIV
  • Rapid change of HA and NA (Vectored>WIV & LAIV)
  • Broader cross-protection (LAIV>RP>WIV)
  • Improved mucosal immunity (LAIV>RP & WIV)

• New computational tools to enhance surveillance and HI data analysis
  • Allows a better understanding of antigenic consequence of changes in the HA.

• Repeatable swine models for VAERD and antigenic imprinting.

• Stronger relationships with CDC, other influenza host sectors, and international networks.
Acknowledgements

NADC
• Tavis Anderson
• Eugenio Abente
• Carine Souza
• Bryan Kaplan
• Jennifer Chang
• Meghan Brand
• Brian Kimble
• Kelly Schiro
• Michael Zeller
• Michelle Harland
• Nick Otis
• Gwen Nordholm
• Rasna Walia

Collaborators
• Phil Gauger
• Marie Culhane
• Gaelle Simon
• Susan Detmer
• Lars Larsen
• Alicia Janas-Martindale
• John Schiltz
• Ellen Kasari
• Nicola Lewis
• Divya Venkatesh
• Daniel Perez
• Nacho Mena
• Randy Albrecht
• Adolfo Garcia-Sastre
• Scott Kraus
• Richard Webby
• Andy Bowman
• Martha Nelson