Variant Influenza Virus Infections in the United States

Carmen Arriola
Influenza Division, Centers for Disease Control and Prevention

The findings and conclusions in this presentation are those of the presenter and do not necessarily represent those of CDC
Influenza

Variant Influenza A Virus Infections

- Non-Human (‘animal-origin’)
- Novel (avian and swine)
- Variant (swine-origin)

Human (Seasonal flu)
- Causes epidemics in people every year
- Mild respiratory illness for most but can be severe
- Vaccine is best protection

- New flu viruses, not circulating in people
- Made when different virus genes mix
- No protection from vaccine or prior infection
- If efficiently transmitted, then pandemic is possible
Variant Influenza A Virus Infections

- Human infections with influenza A virus subtypes different from currently circulating human subtypes (A/H1 and A/H3)
- Swine-origin, double/triple-reassortant viruses with swine, avian, and human influenza genes
- Little to no underlying immunity in human population
  - If efficiently transmitted, then epidemics or pandemic are possible
In 2011 swine-origin viruses were given the name “variant” influenza virus.

Influenza viruses that are known to circulate in pigs are called “influenza viruses—swine” when isolated from pigs, but are called “variant viruses” when isolated from humans.

Variant viruses are designated with the letter “v”:
- An A(H3N2) virus that circulates in pigs and is isolated from a human would be called “A(H3N2) variant” or “A (H3N2v)”.

The sole requirement for a virus to be termed variant is that it be a swine origin influenza virus isolated from a human:
- A variant virus may or may not have the M gene from the influenza A (H1N1)pdm09 virus, along with other genetic changes.

“Variant” is not used for influenza viruses from animals other than pigs.
Influenza A Viruses in US Swine

- Swine influenza virus (IAV-S)
  - Causes respiratory symptoms
  - Secondary bacterial infections common
  - Often mild illness; not often fatal
- Endemic in pig herds
  - Seroprevalence 50–90%
  - Cause annual epidemics
  - Commercial herds often vaccinated
- Common subtypes:
  - H1N1, H1N2, H3N2
Why Focus on Swine-Origin Influenza?

• Influenza virus attachment to host cells mediated by sialic acid-galactose link
• Human-origin virus: (α 2,6) linkage
• Avian-origin virus: (α 2,3) linkage
• Swine-origin virus: (α 2,6), (α 2,3) linkages
• Pigs may act as “mixing vessels” for reassortment of avian, human, and swine origin viruses

Variant Influenza Virus Infections in the United States

- 375 Cases
- 30 Hospitalizations
- 2 Deaths
Subtypes of US Variant Influenza A Cases, 2005–2015
2012 H3N2V OUTBREAK
Epi-Curve for Confirmed Cases of H3N2v, July - September, 2012 (N=306)

Estimated number of fairs in US

(Includes illness onset dates imputed from specimen collection dates only)
# H3N2v Case Count
## July 9 – September 7, 2012

<table>
<thead>
<tr>
<th>State</th>
<th>Number of confirmed cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawaii</td>
<td>1</td>
</tr>
<tr>
<td>Illinois</td>
<td>4</td>
</tr>
<tr>
<td>Indiana</td>
<td>138</td>
</tr>
<tr>
<td>Maryland</td>
<td>12</td>
</tr>
<tr>
<td>Michigan</td>
<td>6</td>
</tr>
<tr>
<td>Minnesota</td>
<td>4</td>
</tr>
<tr>
<td>Ohio</td>
<td>107</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>11</td>
</tr>
<tr>
<td>West Virginia</td>
<td>3</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>306</strong></td>
</tr>
</tbody>
</table>
H3N2v Epidemiology I
National Outbreak Cases

- Cases were young
  - Median age = 7 years
  - 92% < 18 years
- Symptoms were mostly mild
  - Only 16 hospitalizations
    - 11/16 were high-risk patients
  - 1 death in a high-risk patient
- Person-to-person transmission was limited
  - 15 cases with person-to-person transmission
  - No evidence of sustained or community transmission
H3N2v Epidemiology II

National Outbreak Exposures

• Cases were exposed to swine at agricultural fairs
  • 90% attended a fair
  • 98% had swine contact

• Prolonged, close contact with swine....
  • > 50% with multiple days of contact
  • ≈ 30% with 7 days of contact
PUBLIC HEALTH RESPONSE TO H3N2V
Novel Influenza A Virus Surveillance

• Since 2005, public health labs provided with RT-PCR procedures and training for detection of variant A/H1, A/H3 and avian H5N1, H7N9 viruses

• In 2007, novel influenza A infections added to the National Notifiable Diseases Surveillance System (NNDSS)
2012-2013 H3N2v Case Definitions

**Confirmed:** Influenza A (H3N2)v virus infection in a patient with test results consistent with influenza A (H3N2)v (InfA, H3, and pdmInfA positive results, and H1 and pdmH1 negative results on RT-PCR)*

**Case Under Investigation:** Illness compatible with influenza in a patient meeting at least one of the epidemiologic criteria below for whom laboratory confirmation is not known or pending, or for whom test results do not provide a sufficient level of detail to confirm influenza A (H3N2)v virus (e.g., a positive rapid influenza diagnostic test)

-Recent close contact (within 7 days of illness onset) with confirmed cases of influenza A (H3N2)v virus infection

**OR**

-Recent contact (within 7 days of illness onset) with swine or recent attendance at an event (such as an agricultural fair) where swine were present

*Or H3N2v positive by CDC RT-PCR or genetic sequencing
Novel Influenza A Case Reporting

- Case illness onset
  - Days to weeks

- State HD identifies positive specimen
  - Days to weeks

- State HD notifies CDC, sends specimen for confirmation
  - 24 to 48 hours

- State HD interviews case(s) and submits CRF(s) to CDC
  - 2 to 3 days

- State HD conducts contact tracing for confirmed cases and looks for additional epidemiologically-linked cases
  - Days to weeks

- State HD may request assistance with a field investigation
  - Days to weeks
CDC Influenza Division identifies or receives report of possible human infection with novel influenza A virus

- Virus specimen undergoes laboratory testing for confirmation
- CDC begins epidemiologic investigation with State and Local Health Departments
- CDC notifies agency and extra-agency partners, including State and local public health partners, Animal and agricultural health partners, International partners, Federal public health partners

**Laboratory**
- Virus confirmed as novel influenza A
- Virus characterized for resistance, severity and transmissibility
- Implementation of initial containment and/or mitigation measures

**Epidemiology**
- Parallel animal health investigation conducted by animal health partners as appropriate
- Objectives of epidemiologic investigation:
  1. Evaluate person-to-person transmission
  2. Characterize severity, magnitude, scope of illness/outbreak
  3. Identify risk factors for illness

**Communications**
- Ongoing communication with CDC, State and Local Health Departments, extra-agency partners

- Results of investigation do not indicate sustained human-to-human transmission of novel influenza A
- Novel A investigation concluded

- Results of investigation indicate sustained human-to-human transmission of novel influenza A
- Novel A investigation expanded; evaluate for pandemic potential
# National Case Reporting

## Contributions and Limitations

<table>
<thead>
<tr>
<th></th>
<th>Contributions</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| National case reporting | • Relatively detailed case information  
                        | • Descriptive data from every variant case identified | • Delayed “event detection”  
                        |                                                  | • Underestimate of true number of cases  
                        |                                                  | • Risk assessment difficult                  |
Public Health Response Communications

Press Briefing Transcript

CDC Telebriefing: Influenza A (H3N2) Variant Virus
Friday, August 3, 2012, Noon ET

This is an official CDC HEALTH ADVISORY

Variant Influenza Virus (H3N2v) Infections

Summary: This Health Alert Network Health Advisory provides an update on H3N2 variant virus (or "H3N2v") activity and summarizes CDC’s updated H3N2v case definitions and recommendations for H3N2v surveillance for the summer and fall of 2013. It supersedes the last H3N2v-related HAN Health Advisory, HAN 325, which was issued August 3, 2012.

July

CDC Reports Cases 14-17 of H3N2v Infection; Shares Advice for Safe Fair-Going
July 26, 2012

CDC today reported the first fair-associated outbreak of influenza A (H3N2) variant virus this year. Genetic testing at CDC has confirmed that viruses found in humans and those found in swine in this situation are nearly identical. Fairs are an important event for exhibitors and their swine, and a great experience for fairgoers, but the detection of H3N2v at a few fairs last year, and the re-emergence at one fair so far this year...
Public Health Response
Communications

• Information online at
  http://www.cdc.gov/flu/swineflu/h3n2v-cases.htm
H3N2v Vaccine Development

• Candidate vaccine virus identified (A/Minnesota/11/2010)
• Clinical investigational lots of inactivated subunit H3N2v vaccine have been made by manufacturers
• After comprehensive analysis of anticipated burden of H3N2v and impact of vaccine, decision made to not produce vaccine
• Clinical trials using the NIH’s Vaccine and Therapeutics Evaluation Unit (VTEU) are underway
Prevention of Variant Influenza I

• Get seasonal influenza vaccination
• Avoid contact with sick animals
• Infectious animals can look healthy
• Minimize unnecessary contact with animals at fairs
• Stay away from animals when you are sick
• Wash hands after contact with animals, contaminated equipment, or surfaces
Prevention of Variant Influenza II

- People at high risk for influenza complications should avoid swine & swine barns at fairs
  - 65 years and older
  - <5 years of age
  - Underlying medical condition
- Avoid eating, drinking, and smoking in animal areas
- Cover pacifiers, bottles, and sippy cups before entering animal areas
- Limit stroller and wheelchair use in animal areas if possible
Outreach to Agricultural Fairs

- Educational signage
- Measures to Minimize Influenza Transmission at Swine Exhibitions

For your health and safety, please stow strollers here before entering.

Reduce your risk:

1. Wash your hands before and after touching the animals or their environment.
2. No “hand to mouth” contact, such as eating, smoking and nailbiting.
3. Use special caution if you are pregnant, elderly or have children under 5.

PREVENT THE SPREAD OF FLU BETWEEN PEOPLE AND PIGS AT FAIRS

Pigs can be infected with their own influenza viruses. Careful handwashing is imperative. People possessing flu viruses, especially from contact with pigs. This has happened in outbreaks among people handling pigs.

Issues for Fair Organizers to Consider When Planning Fairs

- Use signage and messaging to educate attendees about influenza prevention and animal care.
- Encourage fair organizers to develop and implement strategies to minimize transmission risks.
- Provide information on proper hygiene practices for participants and visitors.

document (May 2013)
Education of Highly Exposed Groups

• Agricultural youth have extensive animal exposure and may be at increased risk for variant influenza
• CDC and USDA began collaboration in 2012
• Establish relationships with 4-H, FFA, NFU
  • Reduce morbidity and mortality associated with zoonotic diseases
  • Facilitate early detection of emerging diseases such as variant influenza
  • Understand role of public and animal health in disease prevention
AVIAN OUTBREAKS 2014-15
Infection Risk for persons exposed to HPAI A H5 virus infected birds, USA, December 2014-March 2015

Arriola et al 2015 EID
EXTRA SLIDES
# H3N2v RT-PCR Interpretation

<table>
<thead>
<tr>
<th>InfA</th>
<th>H1</th>
<th>H3</th>
<th>pdm InfA</th>
<th>pdm H1</th>
<th>RP</th>
<th>Result Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>Influenza A Detected; Presumptive positive for Influenza A(H3N2) variant virus</td>
</tr>
</tbody>
</table>
# National Case Reporting
## 2012 H3N2v Outbreak Epidemiologic Parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=306 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>47%</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>7 (1 month–74 years)</td>
</tr>
<tr>
<td>White</td>
<td>97%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever/feverishness</td>
<td>98%</td>
</tr>
<tr>
<td>Cough</td>
<td>85%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>83%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>68%</td>
</tr>
<tr>
<td>Headache</td>
<td>67%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>61%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25%</td>
</tr>
<tr>
<td>Eye irritation/redness</td>
<td>23%</td>
</tr>
</tbody>
</table>

Received antiviral treatment: 170/281 (60%)
Received influenza vaccination in past year: 135/244 (55%)
Sought healthcare for illness: 282/293 (96%)
Hospitalized: 16 (5.2%)
Fatal: 1 (< 1%)
## National Case Reporting
### 2012 H3N2v Outbreak Epidemiologic Parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=306 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure Characteristic</strong></td>
<td></td>
</tr>
<tr>
<td>Agricultural fair attendee</td>
<td>90%</td>
</tr>
<tr>
<td>Direct contact with swine</td>
<td>75%</td>
</tr>
<tr>
<td>Direct contact with swine at fair</td>
<td>95%</td>
</tr>
<tr>
<td>Direct contact with swine at farm</td>
<td>32%</td>
</tr>
<tr>
<td>Indirect contact with swine</td>
<td>23%</td>
</tr>
<tr>
<td>Indirect contact with swine at fair</td>
<td>97%</td>
</tr>
<tr>
<td>Indirect contact with swine at farm</td>
<td>7.9%</td>
</tr>
<tr>
<td>No swine contact</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Number of days with swine contact in week prior to illness</strong></td>
<td></td>
</tr>
<tr>
<td>1 Day</td>
<td>35%</td>
</tr>
<tr>
<td>2—3 Days</td>
<td>18%</td>
</tr>
<tr>
<td>4—6 Days</td>
<td>20%</td>
</tr>
<tr>
<td>7 Days</td>
<td>27%</td>
</tr>
<tr>
<td>Estimated incubation period, mean days (95% confidence interval)</td>
<td>2.9 (2.7—3.1)</td>
</tr>
<tr>
<td>Illness duration, median days (range)</td>
<td>5 (1—16)</td>
</tr>
<tr>
<td>Household size, median (range)</td>
<td>4 (1—12)</td>
</tr>
<tr>
<td>Underlying medical condition</td>
<td>23%</td>
</tr>
</tbody>
</table>
2012 H3N2v Laboratory Summary

• 126 viruses sequenced were 93%-100% identical in all genes

• Phylogenetic analysis of 104 viruses showed:
  — M gene from pdm09 H1N1
  — 7 gene segments similar to triple-reassortant H3N2 SIV

• Limited pre-existing population immunity to H3N2v

• Limited cross-reactivity to seasonal vaccine
  — Seasonal vaccine not expected to confer immunity

• All 117 H3N2v isolates tested were sensitive to zanamivir, oseltamivir, and peramivir
2012-2013 H3N2v Enhanced Surveillance Recommendations

- RT-PCR testing critical
- Contact tracing of confirmed cases essential
- Specimen collection from:
  - All ILINet providers
  - ILI outbreaks, particularly among children in child care and school settings (these settings were associated with person-to-person H3N2v transmission in 2011)
  - Unusual or severe presentations of ILI, including hospitalized persons
  - Medically attended ILI and ARI in areas where confirmed H3N2v cases have occurred and from persons with recent agricultural fair or swine exposure
H3N2V LABORATORY DATA
The pdm09 H1N1 Matrix (M) Gene “Recent Cases”

1998 – 2009 triple reassortant influenza A (H3N2) viruses

2011-2013 variant influenza A (H3N2)v viruses

2009 pandemic influenza A (H1N1) viruses

HA denotes the hemagglutinin gene, NA the neuraminidase gene, PB1 the polymerase PB1 gene, PB2 the polymerase PB2 gene, PA the polymerase PA gene, NP the nucleocapsid protein gene, M the matrix protein gene, and NS the nonstructural protein gene.
The pdm09 H1N1 Matrix (M) Gene

1) The M gene contributes to efficient transmission of pH1N1 in animal models

2) M gene may contribute to increased transmission of H3N2v but other factors would likely also be involved
Proportion of Persons with Hemagglutination Inhibition Antibody Titer $\geq 40$ to Influenza A (H3N2)v Virus by Year of Birth

![Graph showing the proportion of persons with hemagglutination inhibition antibody titer $\geq 40$ to influenza A (H3N2)v virus by year of birth. The graph includes data from NORWAY (A/Indiana/08/2011), CANADA (A/Ohio/13/2012), and USA (A/Indiana/10/2011). Birthday years 2011, 2001, 1991, 1981, 1971, 1961, 1951, 1941, 1931, 1921, 1911 are shown along the x-axis. The y-axis represents the proportion ranging from 0 to 100.]

Birth Year

0 25 50 75 100


Proportion

10 year-olds 50 year-olds 30 year-olds

Patterns of antibody expressions to H3N2v potentially explained by cross reactivity to A/Beijing/32/1992
H3N2 and H3N2v Antibody Expression Among Healthy Individuals

Courtesy of Xiuhua Lu and Feng Liu

NHANES 2010 (N=273); age 6-95 in 4-yr intervals for persons born after 1969; ~10-yr intervals for those born before 1969. 10-36 persons/age group