Public Health Response to Severe Seasonal Influenza

A 508 compliant video is available at: https://youtu.be/azcMZCCr7E
Influenza – Historical Perspective

- From medieval Italian meaning “influence”
  - Originally referring to the astrological influence of the stars
  - Later became *influenza del freddo*, “influence of the cold”

- Epidemics each season, pandemics periodically
  - Historians attribute influenza as the cause of pandemics going back centuries
  - Two modern pandemics achieving milestones in 2018
    - 1918 “Spanish” Pandemic (H1N1) – 100 years
    - 1968 “Hong Kong” Pandemic (H3N2) – 50 years

- Persistence through plasticity
  - The influenza virus has evolved to evade human immunity
  - Constant changes allow adaptation

Influenza Virus

- **Current influenza viruses of humans**
  - Influenza A(H3N2)
  - Influenza A(H1N1)pdm09
  - Influenza B/Yamagata
  - Influenza B/Victoria

- **Important outer surface proteins**
  - Hemagglutinin – Vaccines induce antibodies to block this protein
  - Neuraminidase – Antiviral drugs inhibit this protein
Significant Annual Burden of Influenza

United States
- Deaths: 12,000 – 56,000
- Severe Cases: 140,000 – 710,000
- Hospitalizations: 9.2M – 35.6M

Global
- Deaths: 291,000 – 646,000
- Severe Cases: 3M to 5M
- Hospitalizations: 1.0 B

Direct Medical Costs: $10.4 B per year
Indirect and Direct Costs: $87.1 B per year

Influenza Impact Varies by Season, Highest with H3N2

Estimated Cases, Care-Seeking Cases, and Hospitalizations, U.S. 2010-17 Seasons

- Hospitalizations
- Cases

Number of Hospitalizations

- A(H3)
- B
- A(H1)pdm09

Number of Cases

- 2010-11
- 2011-12
- 2012-13
- 2013-14
- 2014-15
- 2015-16
- 2016-17

CDC. https://www.cdc.gov/flu/about/disease/2015-16.htm
Impact of Current Season

Colorado Among Worst Hit States For Flu Cases

By Jamie Leary

WELD COUNTY, Colo. (CBS4) - The Centers for Disease Control says the flu is now widespread in every state except Hawaii.

Severe flu in California brings medicine shortages, kills 27

Alabama declares state of emergency due to widespread flu cases

Posted: Jan 11, 2018 6:41 PM EST
Updated: Jan 11, 2018 7:01 PM EST
By WALA Webstaff

HOSPITALS SWAMPED WITH FLU CASES

BREAKING NEWS
FLU ALERT
WIDESPREAD OUTBREAK ACROSS ALABAMA
LOTTERY 2-8-16 08-19-20-24-27-1
Public Health Surveillance for Influenza in the U.S.

- Surveillance Systems
  - Virus Surveillance
  - Geographic Spread
  - Outpatient Illness
  - Hospitalizations
  - Mortality
Virus Surveillance Shows H3N2 Is Predominant

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season

- **H3N2 Infections**
  - Of all Flu+ (12,474):
    - 78%
  - Of all Flu A+ (10,874):
    - 90%

- H1N1 and B continue to increase

- No evidence of resistance to antiviral drugs among 555 H3N2 viruses tested

CDC FluView. https://www.cdc.gov/flu/weekly/index.htm; 28,264 specimens tested,
Influenza Is Widespread in 49 States

Weekly Influenza Activity Estimates Reported by State & Territorial Epidemiologists*
Week ending January 6, 2018 - Week 1

Influenza-Like Illness Is Earlier With Rapid Increase in Visits

- 339,598 visits for ILI reported this season
- Current season tracking closely to past H3N2 seasons:
  - 2014-15
  - 2012-13
Highest Influenza-Like Illness reported in South and West

Hospitalizations Tracking with Recent H3N2 Seasons

Cumulative Number of Laboratory-Confirmed Influenza Hospitalizations, 2011-2017 Seasons

Current season consistent with recent H3N2 seasons

Hospitalization Rate per 100,000

Twenty Influenza-Associated Pediatric Deaths Reported

Influenza-Associated Pediatric Deaths, 2014-15 Season to Present

- **2014-2015**: Number of Deaths Reported = 148
- **2015-2016**: Number of Deaths Reported = 92
- **2016-2017**: Number of Deaths Reported = 110
- **2017-2018**: Number of Deaths Reported = 20
Conclusions

- Influenza A(H3N2) is predominating this season in the U.S.
  - Influenza A(H1N1) and influenza B starting to increase

- Influenza activity began early and has risen quickly
  - Consistent with past H3N2 seasons: 2012-13 and 2014-15

- H3N2 seasons have been associated with higher numbers of influenza cases, hospitalizations and deaths
  - Influenza-associated hospitalization rates this season appear similar to recent H3N2 seasons
The Problem of H3N2

David Wentworth, PhD

Chief, Virology, Surveillance, and Diagnosis Branch
Influenza Division
National Center for Immunization and Respiratory Diseases
Influenza Viruses Survive On The Edge of Catastrophe

- Replication of influenza viruses is error-prone
  - Disadvantage for the virus
    - Close to the threshold of extinction (e.g., many defective viruses)
  - Advantages for the virus
    - Increased adaptability, variants are rapidly selected upon any type of evolutionary pressure (e.g., antiviral drugs, new host, immune)
    - Evolutionary benefit for evading host immunity

- Influenza survives as a population of viruses, not as a single virus

- Influenza viruses, especially H3N2, are constantly changing
  - Requires continuous comprehensive virus surveillance
  - Necessitates frequent updates to the vaccine
Evaluation of Influenza Viruses at CDC

- **Genetic Characterization**
  - Segmented genome (enables reassortment)
  - CDC uses next-generation sequencing of influenza genome
  - Detects all variation – only some are significant changes

- **Antigenic Characterization**
  - CDC uses multiple tests to evaluate changes in the hemagglutinin surface protein to monitor:
    - Changes in circulating viruses, “drift”
    - Evasion of host immunity to prior infection or vaccination

- **Vaccine virus selection**
  - Twice annual review of analysis on thousands of viruses
  - Choose one each of A(H3N2), A(H1N1), B/Yamagata, B/Victoria
Vaccine Viruses Need to be Selected Six Months in Advance

Northern Hemisphere (NH) Vaccine Viruses Selected in February each year

A(H3N2) A(H1N1) B/Yamagata B/Victoria

Make Vaccine

Vaccinate
Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

- H3N2 Viruses Evolve More Rapidly than Other Influenza Viruses
- H3N2 has required twice the number of vaccine viruses changes than H1N1
- CDC surveillance shows several H3N2 genetic groups co-circulating this season

**Epitope Changes**

- Number of significant changes to important regions of the hemagglutinin gene
- \( \times \) = Vaccine Viruses
Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

Epitope Changes

- Number of significant changes to important regions of the hemagglutinin gene

X = Vaccine Viruses

Most common in Australia over summer
Most common in U.S. this season

CDC collaboration with NextFlu. Neher, Bedford et al.
Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

97% of circulating H3N2 viruses are similar to the cell-propagated H3N2 reference viruses representing the virus used in the vaccine this season in the U.S.
Antigenic Characterization of H3N2 Viruses is Increasingly Difficult
Antigenic Characterization of H3N2 Viruses is Increasingly Difficult

Circulating Viruses

Respiratory Specimen from Flu Patient

Virus Culture in Cells

Cell-Propagated Reference Virus

Antigenic Characterization

New methods required for propagating H3N2 viruses in cell culture
Antigenic Characterization of H3N2 Viruses is Increasingly Difficult

Recent H3N2 viruses require additional and new tests
• Focus-reduction and microneutralization assays
• Developing “nano-neutralization” assay
Influenza Vaccine Manufacturing Requires Specially Prepared Viruses

- **Egg-Based Influenza Vaccines**
  - Primary manufacturing technology for over 50 years
  - Majority (~87%) of available vaccines in the U.S. use eggs
  - CDC and other laboratories isolate viruses directly from human respiratory specimens in eggs
    - Influenza viruses can undergo changes as they are grown in eggs

- **Influenza Vaccines Made Without Eggs**
  - Cell-Based Manufacturing
    - CDC provides cell-propagated candidate vaccine viruses to the cell-based manufacturer
  - Recombinant Protein Manufacturing
    - CDC provides gene segment sequences to manufacturer which then generates protein using insect cells
H3N2 Virus Growth in Eggs Is Increasingly Challenging

- **Poor Propagation**: H3N2 viruses are difficult to propagate in eggs.
- **Egg Propagation Can Change Antigenicity**: Contemporary H3N2 (3C.2a) viruses acquire changes on the hemagglutinin protein upon propagation in eggs and this can impact the antigenic properties.
Cell-Propagated H3N2 Reference Viruses Show Limited Antigenic Drift Compared to Circulating H3N2 Viruses

Reactivity of circulating viruses to ferret anti-sera raised against cell-propagated or egg-propagated viruses representing the 2017-18 H3N2 vaccine virus
Egg-Propagated H3N2 Reference Viruses Are Less Similar to Circulating H3N2 viruses Than Cell-Propagated

Reactivity of circulating viruses to ferret anti-sera raised against cell-propagated or egg-propagated viruses representing the 2017-18 H3N2 vaccine virus
H3N2 Summary

- H3N2 viruses rapidly evolve and evade immunity generated from prior exposure and or vaccines
  - Many divergent populations are co-circulating
  - H3N2 changes rapidly to adapt to selective pressures

- Efforts are underway to overcome contemporary H3N2 vaccine challenges
  - Improving virus strain selection
    - Increased use of Next-Generation sequencing and fitness forecasting
    - Development of new assays
  - Manufacturers employing new technologies
    - Cell-propagated vaccine viruses
    - Recombinant protein vaccines
Mitigating Influenza with Vaccines and Antivirals

Alicia Fry, MD, MPH
Chief, Epidemiology and Prevention Branch
Influenza Division
National Center for Immunization and Respiratory Diseases
Influenza Vaccination

- Influenza vaccination is recommended for all persons aged 6 months and older *each year*
- The 2017-18 influenza vaccine contains a similar H3N2 virus as last season, only the H1N1 virus was updated

**2017-18 Influenza vaccine composition:**
- A/Michigan/45/2015 (H1N1)pdm09-like virus (updated);
- A/Hong Kong/4801/2014 (H3N2)-like virus (same)
  - B/Brisbane/60/2008-like virus (same)
- B/Phuket/3073/2013-like virus (same, only in quadrivalent)
We monitor influenza Vaccine Effectiveness (VE) every year with the US Flu VE Network

**US Flu VE Network***

<table>
<thead>
<tr>
<th>Season</th>
<th>VE against A/B influenza viruses (95% CI)</th>
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<tbody>
<tr>
<td>2010-11</td>
<td>60% (53, 66)</td>
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<tr>
<td>2011-12</td>
<td>47% (36, 56)</td>
</tr>
<tr>
<td>2012-13</td>
<td>49% (43, 55)</td>
</tr>
<tr>
<td>2013-14</td>
<td>52% (44, 59)</td>
</tr>
<tr>
<td>2014-15</td>
<td>19% (10, 27)</td>
</tr>
<tr>
<td>2015-16</td>
<td>48% (41, 55)</td>
</tr>
<tr>
<td>2016-17</td>
<td>40% (32, 46)</td>
</tr>
</tbody>
</table>

*Enrolls outpatients aged >6 months old with acute respiratory illness from 66 clinics. Uses a test-negative case-control design where PCR positive flu = case and PCR negatives = control

https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm
Last Season (2016-17), Vaccination Reduced Influenza-Associated Outpatient Visits by 40%

https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm
Vaccine Effectiveness Varied By Vaccine Component Last Season

Vaccine Effectiveness, U.S. 2016-17 Season

- A/B: 40%
- A/H3N2: 33%
- All B Age group: 53%
- B/Victoria: 56%
- B/Yamagata: 52%

https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm
In recent years, the H3N2 vaccine component has not worked as well as H1N1 or B vaccine components.

- Meta-analysis of observational VE studies conducted in ambulatory care settings, 2004-2015

  - Pooled VE against influenza B viruses was 54%
  - Pooled VE against influenza A(H1N1)pdm09 viruses was 61%
  - Pooled VE against H3N2 viruses was 33%
Current influenza vaccines reduce the burden of illnesses in the US

- In 2016-17, vaccination provided substantial prevention:

  - 84,600 Hospitalizations
  - 2.6 million Outpatient Visits
  - 5.3 million Illnesses

Modeled using estimates of disease burden, vaccine coverage and effectiveness, based on Reed et al https://www.cdc.gov/flu/about/disease/2015-16.htm
Our second line of defense after vaccination: antiviral medications for treatment of influenza

3 FDA-approved neuraminidase inhibitors* (NAIs) are recommended

- Oral oseltamivir (Tamiflu® or generic formulation)
  - Approved for treatment age ≥14 days (recommended for all ages)
- Inhaled zanamivir (Relenza®)
  - Approved for treatment age ≥7 years
- Intravenous peramivir (Rapivab®)
  - Approved for treatment age ≥2 years

*Only medications active against circulating influenza viruses. Not effective against other viruses.
Evidence for neuraminidase inhibitors (NAI) efficacy

- Randomized placebo-controlled clinical trials (RCTs) in outpatients with lab-confirmed influenza:
  - Early treatment (within 2 days of illness onset) shortened duration of fever and illness symptoms by ~1 day

- No placebo controlled clinical trials for prevention of severe outcomes
Evidence for NAI effectiveness against severe outcomes from meta-analyses and observational studies

- Evidence from meta-analyses of RCTs in outpatients and observational studies in hospitalized and outpatients demonstrate that early treatment reduces severe illness

Outpatients with lab-confirmed influenza: Reduction in subsequent otitis media (34%) in children, and lower respiratory tract illnesses requiring antibiotics (37-44%) and hospitalizations (63%) in adults, and reduction of hospitalizations (75%) in high risk persons (all ages)

Hospitalized patients: Reduction in mortality in adults (50%) and shortened length of PICU stay (18%) and post admission mechanical ventilation (34-77%) in children

CDC Antiviral Guidance focuses on severe illness

- **Antiviral treatment is recommended** as early as possible for any patient with suspected or confirmed influenza who is:
  - Hospitalized
  - Has severe, complicated, or progressive illness
  - Is at high risk for influenza complications

- **Antiviral treatment can be considered** for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment
  - If treatment can be initiated within 48 hours of illness onset

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Persons at High Risk for Influenza Complications

- Children <2 years
- Adults >65 years
- Pregnant and postpartum women
- Persons with immunosuppression
- Persons with underlying medical conditions: chronic pulmonary, cardiovascular, renal, hepatic, hematologic, and metabolic disorders (i.e., diabetes), or neurologic/neurodevelopment conditions, morbid obesity
- American Indians and Alaska Natives
- Persons <19 years who are receiving long-term aspirin therapy

https://www.cdc.gov/flu/about/disease/high_risk.htm
Antiviral Supply This Season

- There is adequate national supply to meet the high demands from this season
- Spot shortages have been reported in areas with high influenza activity
  - We are working with manufacturers to address existing gaps
    - CDC has a webpage on antiviral drug supply with manufacturer information for inquiries related to antiviral purchases/availability.
- Consider advising patients seeking to fill prescriptions to call ahead to make sure their pharmacy has the medication (may need to call more than one)

  Antiviral drugs work better the earlier you begin taking them so prompt action is important.
Annual influenza vaccination is the best way to protect against influenza - as long as influenza viruses are circulating CDC recommends vaccination

- A substantial burden of illnesses are averted with current vaccines

Influenza antivirals are an important second line of defense, especially for patients with severe illness and those at increased risk for severe disease
Conclusions

- Influenza is affecting most of the country
- Peak activity may be occurring now, but influenza will circulate for many more weeks
- Urge your friends, family, and patients to get vaccinated if they have not done so yet
- Think flu - treat hospitalized patients and high risk outpatients with influenza antivirals as soon as possible

Public Health Response to Severe Seasonal Influenza