Complications of Influenza

Jennifer A. Shuford, MD, MPH
Department of State Health Services
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Presentation Outline

- Influenza Basics
- Influenza Prevention
- Complications of Influenza
Influenza Basics

• Two main types of influenza virus
  • Influenza A
  • Influenza B
• Cause seasonal flu epidemics every year
• Influenza A
  • Subtypes based on two surface proteins- Hemagglutinin and Neuraminidase
  • Include H1N1 and H3N2
• Influenza B
  • Separated into lineages
  • Include Victoria and Yamagata lineages

Influenza Virus

• Influenza viruses constantly change
• Antigenic drift
  • Accumulation of small genetic changes
  • Reason that epidemics occur every year
  • Some cross protection is likely
• Antigenic shift
  • Large genetic changes
  • Causes pandemics
  • No pre-existing immunity in the population
Epidemiology of Influenza

- Flu viruses circulate year round
- Flu most common during fall and winter in the US
- Flu usually peaks between December and February
- Unpredictable
- Other respiratory viruses also circulate during this time

Peak Month of Flu Activity 1982-1983 through 2017-2018

Transmission of Influenza Virus

- Primarily spread through droplets
- Formed during coughs, sneezes
- Travel 3-6 feet
- Surfaces may be contaminated and allow transmission
- Airborne spread has been shown experimentally

Figure available at: https://www.cdc.gov/flu/about/season/flu-season.htm. Accessed 9/20/2018.

Image courtesy of CDC/Brian Judd
Transmission of Influenza Virus

- Contagious period
  - 1 day before to 5-7 days after symptoms develop

- Children and immunocompromised people may spread virus longer

- Main point: people spread flu before they know they have it and after the symptoms have resolved!

Flu Symptoms

<table>
<thead>
<tr>
<th>Is it a cold or flu?</th>
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</thead>
<tbody>
<tr>
<td><strong>Signs and Symptoms</strong></td>
</tr>
<tr>
<td>Symptom onset</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Aches</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Fatigue, weakness</td>
</tr>
<tr>
<td>Sneezing</td>
</tr>
<tr>
<td>Stuffy nose</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Chest discomfort, cough</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

**Treatment of Influenza**

- Antiviral medicines are available
- Neuraminidase inhibitors
  - Oseltamivir
  - Zanamivir
  - Peramivir
- Reduce symptoms and decrease length of illness by ~1 or 2 days
- Most effective if started within 48 hours
- May be started later than 48 hours if severe illness or high-risk individual
- New antiviral- Baloxavir marboxil

**Prevention of Influenza**

- Prevention is the preferred approach to flu
- Flu diagnostics and treatments have limitations
- Vaccination is the primary prevention strategy for flu
  - Individuals can clean their hands and stay away from sick people as methods of prevention, but it is difficult to control our surroundings
  - Individuals with flu can spread flu before they feel (or look) sick
- Vaccination is a way that people can take initiative to protect themselves before flu season begins
Flu Vaccine

- Formulated as trivalent or quadrivalent vaccine
- Trivalent vaccine contains
  - 2 influenza A viruses
  - 1 influenza B virus
- Quadrivalent vaccine contains
  - Same three viruses as the trivalent
  - Additional influenza B virus
- Vaccine components chosen twice per year

Estimated Range of Annual Flu Burden, US, 2010-2018

Estimated US Flu Burden by Season, US, 2010-2018

Estimated U.S. Influenza Burden, By Season (2010 - 2016)


Influenza-Associated Pediatric Deaths, US, 2015-2019

Image courtesy of CDC/Dr. Fatimah Dawood. COCA call, September 26, 2019.
Vulnerable Populations

- Adults 65 years and older
- Children younger than 5 years old
- Children younger than 2 years old at greatest risk
- Infants <6 months old have highest hospitalization and death rates
- Pregnant women/women up to 2 weeks after delivery
- American Indians and Alaska Natives
- People who live in nursing homes/LTCFs


Vulnerable Populations

- Kidney disorders
- Liver disorders
- Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- People who are obese
- People younger than 19 years of age on long-term aspirin- or salicylate-containing medications.
- People with a weakened immune system due to disease or medications

- Asthma
- Neurologic conditions
- Blood disorders (such as sickle cell disease)
- Chronic lung disease (such as COPD)
- Endocrine disorders (such as diabetes mellitus)
- Heart disease (such as congestive heart failure and coronary artery disease)

Vulnerable Populations

- High-risk populations are more likely to develop complications
- Healthy people develop complications, too
- Majority of children hospitalized for flu are previously healthy
- About ½ of all pediatric flu deaths occur in children without high risk conditions

Complications from Flu

- Moderate Complications
  - Sinus infections
  - Otitis media (middle ear infection)
- Severe Complications
  - Pulmonary complications
  - Neurological complications
  - Musculoskeletal complications
  - Cardiac complications
  - Sepsis

**Moderate Complications - Sinusitis**

- Infection of the paranasal sinuses
- Viral acute rhinosinusitis
- Follows course of viral illness
- Acute bacterial rhinosinusitis
- Symptoms >10 days without improvement
- Common bacteria include:
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*

**Moderate Complications - Acute Otitis Media**

- Infection of the middle ear
- Diagnosed by evidence of acute inflammation of the middle ear/tympanic membrane
- Most common bacteria include:
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
- Very common among kids with influenza
- ~40% of kids <3 years old with confirmed flu

Moderate Complications—Impact on Children

Table 3. Complications, antibiotic treatments, and hospitalizations in 379 children with culture-confirmed influenza illness.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3 years</td>
</tr>
<tr>
<td>Double otitis media</td>
<td>52 (99.7%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (3.5%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>55 (92.8%)</td>
</tr>
<tr>
<td>Referral to emergency department</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

**NOTE:** Data are no. (%) of cases. Data for 2 children with double viral infection were excluded.

* P < .001, for all comparisons between the age groups (chi-square test).
* P < .01, for all comparisons between the age groups (chi-square test).

Severe Complications—Pulmonary

- Influenza virus replicates primarily in the respiratory epithelium
- Can impact respiratory function through:
  - Direct viral infection of the epithelium
  - Lung inflammation due to immune response
  - Secondary bacterial infection
- ~30-40% of hospitalized patients with lab-confirmed influenza are diagnosed with acute pneumonia.


Image courtesy of CDC

Severe Complications - Primary Influenza Pneumonia

- Direct viral infection of the epithelium
- Lung inflammation due to immune response
- Can be very severe
- May lead to ARDS
- Influenza A is primary viral cause of ARDS in adults
- Influenza A and RSV most common viral causes of ARDS in kids


Severe Complications - Secondary Bacterial Pneumonia

- Common complication of influenza
- Especially in older individuals
- Damaged epithelium from influenza:
  - Increases bacterial binding to damaged cells
  - Decreases mucociliary clearance of bacteria
- Most common bacteria:
  - Streptococcus pneumoniae
  - Staphylococcus aureus
  - Streptococcus pyogenes
- May lead to ARDS and sepsis

Severe Complications - Pneumonia

- Differentiation of primary viral vs. secondary bacterial pneumonia
- Did the patient improve after a few days of antivirals?
- Did the patient start to get better and then worsen?
- Did the patient completely recover from influenza and then develop fever/illness a week later?
- Clinical differentiation is not always possible


Image courtesy of CDC/Dr. Thomas Hooten.

Severe Complications - US P&I Data

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System
Data through the week ending September 7, 2019, as of September 19, 2019

Image courtesy of CDC/Dr. Fatimah Dawood. COCA call, September 26, 2019.

25/26
Severe Complications - Other Respiratory Complications

- Exacerbation of chronic pulmonary disease
- Asthma
- COPD
- Laryngotracheitis or tracheobronchitis (croup)
- ARDS
- Respiratory failure


Severe Complications - Neurological Complications

- Influenza-associated encephalitis/encephalopathy (IAE)
- Rapidly progressive encephalopathy associated with decreased LOC occurring within several days of influenza infection
- Guillain-Barre syndrome
- Acute disseminated encephalomyelitis (ADEM)
- Transverse myelitis
- Reye’s syndrome

Image courtesy of CDC

Severe Complications - Musculoskeletal Complications

- Acute viral myositis characterized by
  - Initial viral infection
  - Myalgias
  - Muscle swelling and weakness
  - Dark urine
  - Labs: elevated CK, myoglobinuria
- Complications include rhabdomyolysis and compartment syndrome
- Mechanism unclear, may be direct viral invasion of muscle


Severe Complications - Cardiac Complications

- Association between cardiovascular disease and influenza has been suspected due to:
  - Overlap of peak incidence in winter
  - Increase in CV deaths during flu epidemics
  - Decreased cardiac events after flu shot
  - COPD
- Cardiac complications include
  - Myocarditis
  - Ischemic cardiac events


Image courtesy of CDC
Severe Complications - Cardiac Complications

- Myocarditis
  - Reported in <1%-13% of hospitalized patients with lab-confirmed influenza
  - Variable clinical course and severity
  - Mild enzyme elevations to heart failure
  - Often associated with pericardial effusions
  - Uncertain mechanism
  - Some evidence of direct viral invasion


Severe Complications - Cardiac Complications

- Ischemic heart disease
  - Several large epi studies from around the world show temporal association of flu activity with hospitalizations/deaths from acute MI
  - Two large self-controlled studies showed higher risk of first MI within 3 days-1week after diagnosis of flu
  - Mechanism likely related to inflammation
  - Inflammation known to have role in development of ACS

**Severe Complications - Sepsis**

- Sepsis: "life-threatening organ dysfunction caused by a dysregulated host response to infection"¹
- Can result from viral or bacterial causes
  - Influenza virus
  - Secondary bacterial infection
  - Influenza infection is associated with higher risk of bacterial sepsis²
- Requires aggressive antimicrobial treatment and supportive care to prevent death

**Complications of Influenza**

- Influenza causes yearly epidemics affecting millions of people in the US every year
- There is a wide spectrum of complications associated with influenza
- Prevention is important!


Image courtesy of CDC
Thank you!

Jennifer A. Shuford, MD, MPH
jennifer.shuford@dshs.texas.gov