Influenza Outbreaks in the Real World?

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Medical Microbiologist and Infectious Diseases
Assistant Professor, Lab Medicine, U of Toronto
Protocols are helpful but….

- Real world doesn’t always fit into ‘the box’
  - Declaring an outbreak? Declaring it over?
    - Case definitions
  - Transfers to other facilities/back to LTCF
  - Testing
    - When to test?
    - Which test?
  - Antivirals
    - Empiric initiation?
    - Which antivirals?
Clinical influenza
An overview

- Acute respiratory infection primarily restricted to the airways (nasopharynx to lungs)
- Systemic symptoms can develop
  - immune response & cytokines
- Age-related morbidity & mortality

When to call an outbreak?

- On paper seems straightforward....
- What is the background noise?
- What is the constellation of symptoms?
- Community onset versus nosocomial disease can be ‘blurry’
  - Especially in the absence of a known etiology
- There are risks either way:
  - Generally, time will tell
  - Consider severity
  - Consider the epidemiology/clustering
  - Be transparent in decision making process....and communicate, communicate, communicate (not us versus them!)
  - The goal is to prevent spread to other patients, wards and centres
INDECISION

The mark of the leader is the ability to make decisions.
The mark of the survivor is knowing when not to.
Influenza Outbreak Epi Curve from Senior’s Health

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Comments: The outbreak declared over on 21 Aug/09. No deaths.

Hard to miss, but unfortunately is often more subtle!
Influenza Outbreak Epi Curve from Senior’s Health

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**Comments:** The outbreak declared over on 21 Aug/09. No deaths.

What if it looked like this?
## Senior’s Health Centre 2008 Influenza Outbreak

<table>
<thead>
<tr>
<th>Name</th>
<th>M/F</th>
<th>Year of Birth</th>
<th>Onset date of first symptom (dd/mm)</th>
<th>Abnormal temperature (°C)</th>
<th>Dry cough (new)</th>
<th>Productive cough</th>
<th>Congestion</th>
<th>Poor Appetite</th>
<th>Rhinorrhea</th>
<th>Myalgia</th>
<th>Malaise</th>
<th>Headache</th>
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<td>22/2/2008</td>
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<td>1911</td>
<td>22/2/2008</td>
<td>N</td>
<td>occ.</td>
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<td>27/2/2008</td>
<td>N</td>
<td>occ.</td>
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Outbreaks at North York General/SHC over past few years

- **Case Definition:** Positive lab confirmation or two of the following symptoms: Temperature instability, new or worsening cough, nasal congestion or chest congestion.

- **Case Definition:** cough or shortness of breath **And** One other symptom including a fever >38 or malaise or myalgia or rigors.

- **Case Definition:** A resident with two new respiratory symptoms, or fever and one respiratory symptom

- **Case Definition:** A resident with two new respiratory symptoms with or without fever
What to do about cases not meeting the cases definition?

- It depends....

- In general I would suggest:
  - over-react with isolation/precautions
  - watchful waiting on the decision to extend/end the outbreak ‘end date’
  - Time will tell
What if the epi curve looked like this? What would you do?

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Investigate further….

- Review the case in detail
  - Symptoms
  - Guest ill exposures
  - Compliance with prophylaxis
  - Reason for prophylaxis failure (absorption, Plavix, etc.)

- Get the case tested for flu
  - Require a fast and very sensitive assay...RT-PCR
Clinical Signs and Symptoms Predicting Influenza Infection

Arnold S. Monto, MD; Stefan Gravenstein, MD; Michael Elliott, MD; Michael Colopy, PhD; Jo Schweinle, MD

Table 3. Proportion of Pooled Participants With Baseline Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients With Laboratory-Confirmed Influenza, % (n = 2470)</th>
<th>Patients Who Tested Negative for Influenza, % (n = 1274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (≥37.8°C)*</td>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>Feverishness*</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>Cough</td>
<td>93</td>
<td>80</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>Weakness</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>Sore throat</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Headache</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>Myalgia</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

*Fever was a body temperature of 37°C or higher, whereas feverishness was the patient’s subjective feeling that they had a fever or chill.
Table 5. Multivariate Predictors of Influenza Infection With Sensitivity and Specificity Analyses*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>76.85</td>
<td>49.14</td>
<td>67.79</td>
<td>60.38</td>
</tr>
<tr>
<td>Cough</td>
<td>69.43</td>
<td>60.89</td>
<td>93.24</td>
<td>20.41</td>
</tr>
<tr>
<td>Fever + cough</td>
<td>79.04</td>
<td>48.91</td>
<td>63.81</td>
<td>67.19</td>
</tr>
<tr>
<td>Fever + cough when onset ≤36 h</td>
<td>77.28</td>
<td>51.35</td>
<td>63.32</td>
<td>67.54</td>
</tr>
<tr>
<td>Fever + cough when onset &gt;36 h</td>
<td>85.37</td>
<td>42.33</td>
<td>50.30</td>
<td>80.89</td>
</tr>
<tr>
<td>Fever + cough + nasal congestion</td>
<td>81.45</td>
<td>48.21</td>
<td>59.03</td>
<td>73.94</td>
</tr>
<tr>
<td>Fever + cough + weakness</td>
<td>80.27</td>
<td>47.85</td>
<td>59.80</td>
<td>71.51</td>
</tr>
<tr>
<td>Fever + cough + myalgia</td>
<td>79.11</td>
<td>47.86</td>
<td>61.50</td>
<td>68.52</td>
</tr>
<tr>
<td>Fever + cough + loss of appetite</td>
<td>79.04</td>
<td>47.75</td>
<td>61.38</td>
<td>68.45</td>
</tr>
<tr>
<td>Fever + cough + sore throat</td>
<td>79.02</td>
<td>45.30</td>
<td>55.51</td>
<td>71.43</td>
</tr>
<tr>
<td>Fever + cough + headache</td>
<td>78.69</td>
<td>46.81</td>
<td>59.80</td>
<td>68.60</td>
</tr>
</tbody>
</table>
Laboratory Testing

- Before testing, you should carefully consider whether you ‘care’ more whether it is positive or negative.
  - Need to understand sensitivity/specificity/PPV/NPV for the assay being used.
## Laboratory Diagnosis of Influenza

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Time to Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>1-10 days</td>
<td>Still gold standard(?), requires expertise, provides virus for studies</td>
</tr>
<tr>
<td>Molecular (RT-PCR)</td>
<td>2-4 hours</td>
<td>Becoming gold standard(?), requires expertise &amp; expensive equipment</td>
</tr>
<tr>
<td>Antigen Detection (IF)</td>
<td>2-4 hours</td>
<td>Requires reading expertise &amp; IF microscope</td>
</tr>
<tr>
<td>Antigen Detection (Rapid EIA-like)</td>
<td>15-30 minutes</td>
<td>Widely available, requires little expertise</td>
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In general, specificity in an outbreak setting will be good, i.e., a positive test should be considered a true positive.
Cell Culture
Cell Culture - CPE

Uninfected

Infected
Direct and Indirect FA Tests: Direct Specimen Testing or Culture Confirmation
Enzyme Immunoassays
Directigen Flu A Test
Directigen Flu A+B Assay
## Comparison of Rapid Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Directigen Flu A</td>
<td>67-92%</td>
<td>88-97%</td>
</tr>
<tr>
<td>Directigen Flu A+B</td>
<td>(A) 77-95%</td>
<td>(A) 90-91%</td>
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<tr>
<td></td>
<td>(B) 71-88%</td>
<td>(B) 98-100%</td>
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<tr>
<td>ZstatFlu</td>
<td>57-65%</td>
<td>98-100%</td>
</tr>
<tr>
<td>FLU OIA</td>
<td>62-88%</td>
<td>52-80%</td>
</tr>
<tr>
<td>QuickVue Influenza</td>
<td>73-81%</td>
<td>96-99%</td>
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Prevalence rates were all >18%
Rapid (POC) Tests: Advantages

- Rapid turn around time
- Rapid outbreak identification
- Cost-effective (?)
- Widespread testing available
- Little expertise required
- Can assist with antibiotic and antiviral usage
A Few Practical Comments on Influenza Testing

- Remember....SNout (sensitive negative rules out), SPin (specific if positive rules in)
  - A negative test using an insensitive assay (EIA, DFA) is of no value whatsoever.
- Remember....even tests which take only 15 -180 minutes to perform technically.....can take 3-4 days to get results.
- When it is REALLY important pick up the phone, use couriers/taxis, and pick up the phone again.
  - Who pays?
What if additional cases who don’t meet the full case definition?

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Comments: The outbreak declared over on 21 Aug/09. No deaths.
Influenza control: antiviral medications

- Uses
  - Prophylaxis
  - Treatment
Antiviral medications

M2 Inhibitors

• Amantidine
  - Prophylaxis only (influenza A)
  - Resistance when used for treatment
  - High level of resistance - removed from CDC and PHAC recommendations

Neuraminidase inhibitors:

• Oseltamivir/Tamiflu® (oral)
• Zanamivir/Relenza® (inhaled)
  - Prevent new virion budding by preventing cleavage from Sialic Acid
  - It can be used as treatment and/or prophylaxis for BOTH influenza A and B
  - High cost
  - Relenza isn’t used in children
Antivirals - Treatment

- Treatment with neuraminidase inhibitors
  - Must be taken within 24-48 hours of onset of illness
  - Decrease length of illness by one day
  - Decrease serious complications
    - 55% decrease in post influenza pneumonia
    - 59% decrease in hospitalization in high risk groups
    - Likely decrease in mortality
Antivirals - Prophylaxis

- Prophylaxis with neuraminidase inhibitor
  - Take for duration of exposure
  - Highly effective (70-90%) at preventing symptoms, decreasing viral shedding
  - Can still develop antibodies
  - In the outbreak setting, extremely effective with few failures.
***Really need to know the up-to-date circulating strains and resistance profiles***

- **Predominant virus in community: A/H1N1 or unknown**
  - Age > 7 years and can reliably use a diskhaler
    - Zanamivir if clinically indicated
  - Age 1-7 years or those who cannot reliably use a diskhaler
    - Combined therapy with oseltamivir + amantidine if clinically indicated

- **Predominant virus in the community: A/H3N2 or B**
  - Oseltamivir if clinically indicated and patient > 1 year of age
Figure 2: Laboratory Confirmation of Influenza and Strong Indication to Treat

**Influenza A – no subtype;**
follow Fig. 1

- Subtype available
  - A/H1N1 Positive
    - Age > 7 years and can reliably use a diskhaler
      - Zanamivir if clinically indicated
    - Age 1-7 years or those who cannot reliably use a diskhaler
      - Amantidine if clinically indicated

**Influenza B**

- A/H3N2 or B Positive
  - Oseltamivir if clinically indicated and patient > 1 year of age
‘Non-routine’ Influenza Tests Available to You

- Antigenic characterization is usually undertaken at NML
  - Slow process undertake on a small random sample of overall isolates
- H1 and H3 PCR is available at CPHL
  - Can tell you if H1N1 outbreak or H3N2 outbreak
  - Can also test for novel H1N1 variant
- Molecular/genotypic (PCR) Tamiflu resistance assay is available for the most common resistance mutation.
  - Phenotypic assay is much slower but will detect more mutations.
MEETINGS

NONE OF US IS AS DUMB AS ALL OF US.
Other Practical Challenges

- Residents of LTCF/Retirement Home transferred to hospital during flu outbreak
  - All about communication, common sense and ......more communication
    - involve the PH, facility, hospital MD, LTCF MD, patient/resident, family, etc.
  - Consider:
    - Whether already exposed or not (e.g., ED transfer)
    - Full-care vs self-care/ Retirement home vs LTCF
    - Influenza versus non-influenza (or not confirmed)
Questions?