Emerging Infections: Pandemic Influenza

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Challenges

• The trends of modern society tend to facilitate spread and increase morbidity
  • Travel, urbanization
  • morbidity vs. mortality
• The cost of medical interventions has increased
• An “uncontrolled disease”
Pandemics

• The emergence of an influenza A virus that is novel for the human population
• Recycling of subtypes every 60 years
• Human viruses can reassort with avian and swine viruses
Epidemic Control

• Surveillance
  • WHO’s network of labs
  • Especially in India, Africa, and South America
  • Allows production of vaccines with antigens that closely match the viruses responsible for epidemics

• Vaccine production and distribution
  • Routine use for high-risk populations

• Antiviral therapy
  • Amantadine and Rimantadine
  • Prophylactic effects is equivalent to vaccine for interpandemic periods, but less for newly emerged pandemic strains
Excess Mortality

• How we define and measure the impact of influenza epidemics

• The number of deaths during an epidemic of influenza-like illness in excess of the number expected
  • How do we know which deaths are flu-related?
  • How do we know what number of deaths to “expect?”
Theme 1: School Is Bad For Your Health

- Spring/early summer: seeding
- Summer: low transmission
- September: sharp increase in transmission
- October: peak of transmission
- Winter vacation: decrease in transmission
- February: transmission peaks again
- Ex. 1918, 1957
Theme 2: Waves

- Pandemic viruses produce at least 3 waves before significant antigenic variation can be detected
  - The first wave is the most deadly
- Ex. 1918, 1957, and 1968
1918

- H1N1
- US origin?
- Training camps in US → troop ships → US forces in France → all allied forces
- 675,000 deaths
- “The clinical course of the fatal pneumonia cases suggests that the virus itself possessed a virulence not seen before nor since.” (66)
1918: The W-shaped Curve

FIGURE 1. Pneumonia and influenza mortality by age in certain epidemic years. (From Dauer and Serfling (17).)
Comparison of Excess Deaths

<table>
<thead>
<tr>
<th>Period</th>
<th>Years</th>
<th>No. of excess deaths</th>
<th>Annual average</th>
<th>Crude rate per 100,000 persons</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pandemic</em></td>
<td>1918–1920</td>
<td>675,000</td>
<td>225,000</td>
<td>218.4</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1920–1933</td>
<td>388,400</td>
<td>28,338</td>
<td>23.0</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1933–1957</td>
<td>242,600</td>
<td>10,108</td>
<td>7.5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>1957–1960</td>
<td>115,700</td>
<td>38,567</td>
<td>22.0</td>
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<tr>
<td>Interpandemic</td>
<td>1960–1968</td>
<td>114,900</td>
<td>14,363</td>
<td>7.5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>1968–1972</td>
<td>111,927</td>
<td>27,982</td>
<td>13.9</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1972–1981</td>
<td>198,800†</td>
<td>22,089</td>
<td>10.3</td>
</tr>
<tr>
<td>Interpandemic*</td>
<td>1981–1991</td>
<td>200,000†</td>
<td>20,000</td>
<td>10.0</td>
</tr>
</tbody>
</table>

* Preliminary estimates.
† Approximation.
Critique of excess mortality as a measure of severity

• The mathematical models used to predict the baseline have not been validated
  • Don’t count influenza B virus

• Detection of excess mortality dependent upon synchronous epidemics throughout the country

• Solution? Improve surveillance in representative geographic areas throughout the country
Hospitalizations as an alternative measure of severity

• The peak of hospitalizations lags just 1 wk after the peak of influenza activity
• Easy to access
• More complete and accurate information
  • → Broaden implications for intervention
• There are 10-12 hospitalizations for every pneumonia-influenza death → more sensitive measurement
Age-specific attack rates

• The ones who spread the flu are healthy school children, college students, and employed persons who have many daily contacts and who are more mobile
Age-specific attack rates, cont.

- Those who are most vulnerable (65+ yrs, 5- yrs) are at the end of the transmission chain.
- So immunizing them reduces mortality and morbidity but doesn’t change the course of the epidemic.
- They are the least likely to have generated adequate protection in response to vaccine.
  - Falsey et al.: 61% of hospitalized elderly persons with influenza A virus infection had been currently vaccinated.
Age-specific attack rates, cont.

- Age distributions of attack rates are different for each epidemic
- “The curve for age-specific rates [is] considerably flatter for...interpandemic outbreaks.”
Implications of age-specific attack rates

• 1) No more than 25-50% of the population can be infected with each epidemic
  – Severe illness limits spread, while mild illnesses (seen in interpandemic outbreaks) increased spread even though part of the population is immune
  • → Why attack rates for pandemic and interpandemic periods are similar
Implications of age-specific attack rates

2) School children have the highest attack rates during pandemic and interpandemic periods

- “Children are the main introducers of influenza into the household.”
  - Early stage of epidemic: school children require the most health care; school absenteeism
  - Later stage of epidemic: Preschool children and adults require more health care; employee absenteeism; hospitalizations of persons 65+ yrs

- “Immunization of school children would be effective for epidemic control.”
Implications of age-specific attack rates, cont.

- Morbidity in children justifies universal influenza immunization
- Right now, we limit morbidity to cases of pulmonary conditions
- But almost 50% of children hospitalized because of the flu have major involvement with another organ system
  - Febrile convulsions, encephalopathy, pericarditis, GI problems, myositis, bacterial sepsis, etc.
Control of Epidemics

• It takes 6 months to produce and distribute an influenza vaccine
• Even with exceptional surveillance, it is extremely unlikely that we can produce, distribute, and administer enough vaccines to the entire population before the first wave of a pandemic
• So we have to choose who gets vaccines
Alternative use of vaccines

• High risk populations (65+ yrs, 5- yrs) are not easily accessible within a short period of time

• The population who will experience the highest attack rate (school children) are easily accessible
  – If we prevent spread in this group, we would buy time to produce more vaccine
Or we don’t have to change a thing

- Use a live attenuated cold-adapted flu vaccine instead of the inactivated flu vaccine
  - More effective tool for epidemic control
    - It works better for 3-9 yr olds and works equally well for older students and young adults
    - Produces broader and longer-lasting immunity against subtypes of influenza A
    - Lower cost
    - Lower total morbidity
    - Easier to administer and more acceptable to young children
      - Nose drops or spray
    - Hasn’t been tested in high-risk populations
Why control influenza?

- Flu epidemics severely disrupt the delivery of health care
- We can reduce pain, suffering, and death