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
  - Prophylatic 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

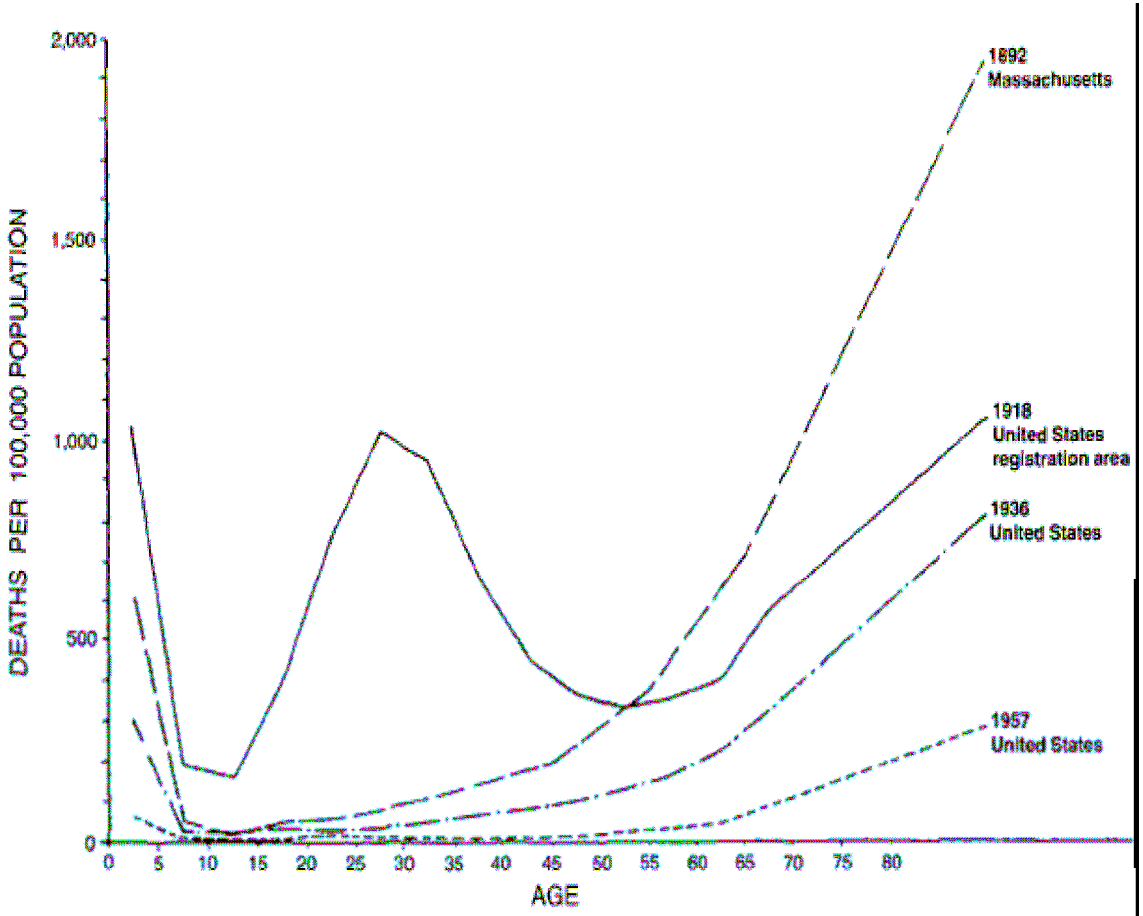

FIGURE 1. Pneumonia and influenza mortality by age in certain epidemic years. (From Dauer and Serfling (17).)

Comparison of Excess Deaths

TABLE 1. Excess deaths estimated for pandemic and interpandemic periods, 1918–1991

Period	Years	No. of excess deaths	Annual average	Crude rate per 100,000 persons
Pandemic	1918–1920	675,000	225,000	218.4
Interpandemic	1920–1933	368,400	28,338	23.0
Interpandemic	1933–1957	242,600	10,108	7.5
Pandemic	1957–1960	115,700	38,567	22.0
Interpandemic	1960–1968	114,900	14,363	7.5
Pandemic	1968–1972	111,927	27,982	13.9
Interpandemic	1972–1981	198,800	22,089	10.3
Interpandemic*	1981–1991	200,000†	20,000	10.0

* 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.

TABLE 2. Age-specific influenza attack rates for pandemic and interpandemic periods 1918–1957

Age (years)	Rates per 100 Persons			
	1918 Pandemic	1928–1929 Interpandemic	Age (years)	1957 Pandemic
<1	20.7	13.8	<5	32
1–4	33.7	24.9		
5–9	39.1	24.8	5–9	33
10–14	38.1	20.0	10–14	52
15–19	34.5	16.3	15–19	54
20–24	32.3	15.7		
25–29	33.7	18.3	20–34	27
30–34	32.6	19.9		
35–39	29.6	19.8	35–39	25
40–44	23.6	18.6	40–44	18
45–49	20.7	17.2	45–49	17
50–54	17.5	16.9	50–54	19
55–59	16.2	16.4	55–59	17
60–64	14.3	16.9		
65–69	13.5	17.5	≥60	10
70–74	11.1	18.1		
≥75	8.8	17.9		
Rate for total	29.4	18.9		24

- 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