The Spanish Flu in US Forces and the Modern Response to Surveillance

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Disclaimer

- The views presented are those of the speaker and do not necessarily represent the views of the DoD, the Department of the Air Force, or the Department of the Army

Emergency hospital during 1918 influenza epidemic, Camp Funston, Kansas. Source: http://www.vaccineinformation.org/photos/flu_afp00

Background

- The influenza pandemic of 1918 killed more people than died in World War I.

- True. WWI casualties estimated at 16 million. 1918 influenza epidemic casualties estimated at 50 million (some estimate 100 million).
- Army: > 1 million hospitalized, >44,000 deaths
- Navy: ~5,000 deaths

- Death rate was 25% higher in Army population than civilian population of the US

http://www.history.navy.mil/library/online/influenza%20pan.htm

What is influenza?

- Acute, usually self-limited illness caused by influenza type A or B, outbreaks every winter
- Attack rates 10-40% over peak 5-6 week period
- Fever, malaise, cough

- Unique among respiratory viral infections:
  - Epidemic nature
  - Associated mortality

Principles and Practices of Infectious Diseases. Mandell, Douglas, and Bennett's, 8th ed.

History

- Outbreaks every 1-3 years for at least 400 years
- Greatest pandemic in history 1918-1919
  - >500,000 deaths in US
- Modern understanding: isolation of influenza A in 1933, influenza B in 1939
- Discovery of growth in chicken eggs facilitated research, vaccine development
- First inactivated vaccines developed in 1940s
- First live attenuated flu vaccine licensed 2003

Impact: Mortality

- Epidemics associated with increased morbidity and mortality, much due to complicating pneumonia
- 20-50,000 excess deaths/year in US
  - Ebola: ~11,000 (largest known outbreak; 1 in US)
  - MERS-CoV: ~ 500 (last 3 years)
  - SARS: 775 deaths worldwide
  - AIDS: ~15,000 deaths in US/year
  - Suicide: 41,000
- Influenza and pneumonia together #1 infectious cause of death in US
- 114,000 hospitalizations/year in US

Classification

- Orthomyxoviridae: A, B, C
- All share certain features: host-cell derived envelope, glycoproteins required for cell entry/exit, negative-sense RNA
- Standard nomenclature:
  - Type (A, B, C)
  - Place of initial isolation
  - Strain designation
  - Year of isolation

Ex: A/Puerto Rico/8/34

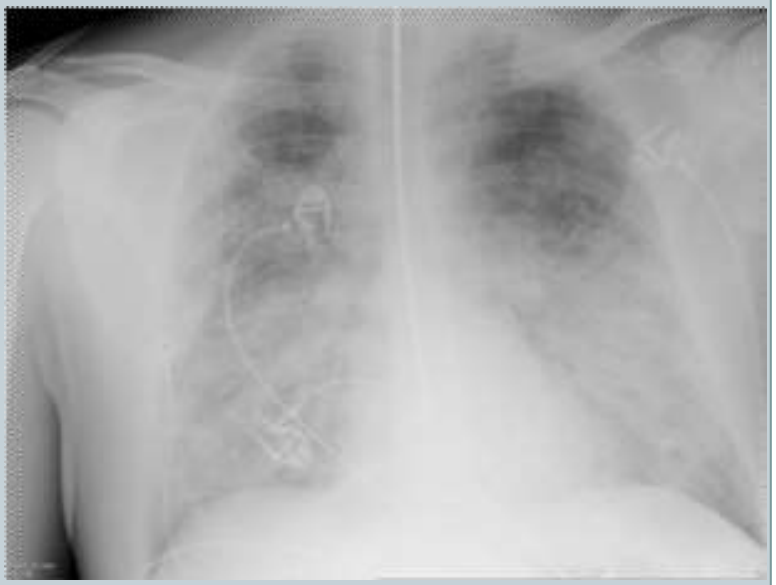
- Influenza A further subtyped on hemagglutinin, neuraminidise activity (e.g. H1N1, H3N2)

Impact: Morbidity

- Estimated in US/year:
  - 13.8-16.0 million excess respiratory illnesses in <20 yo
  - 4.1-4.5 million >20 yo
- Typical case associated with:
  - 5-6 days restricted activity
  - 3-4 days in bed
  - 3 days lost from work or school
- Economic impact due to lost productivity:
  - Per 100 schoolchildren, 37 lost days of school, 20 days missed work by parents

Influenza complications

- Pneumonia most common
  - Primary influenza pneumonia
  - Secondary bacterial pneumonia
- Myositis/rhabdomyolysis
- Central nervous system disease
  - Encephalopathy/encephalitis
  - Transverse myelitis
  - Aseptic meningitis
  - Guillain-Barré syndrome
- Cardiac complications
  - Acute myocardial infarction/unstable angina
  - Myocarditis/pericarditis



www.antimicrobe.org

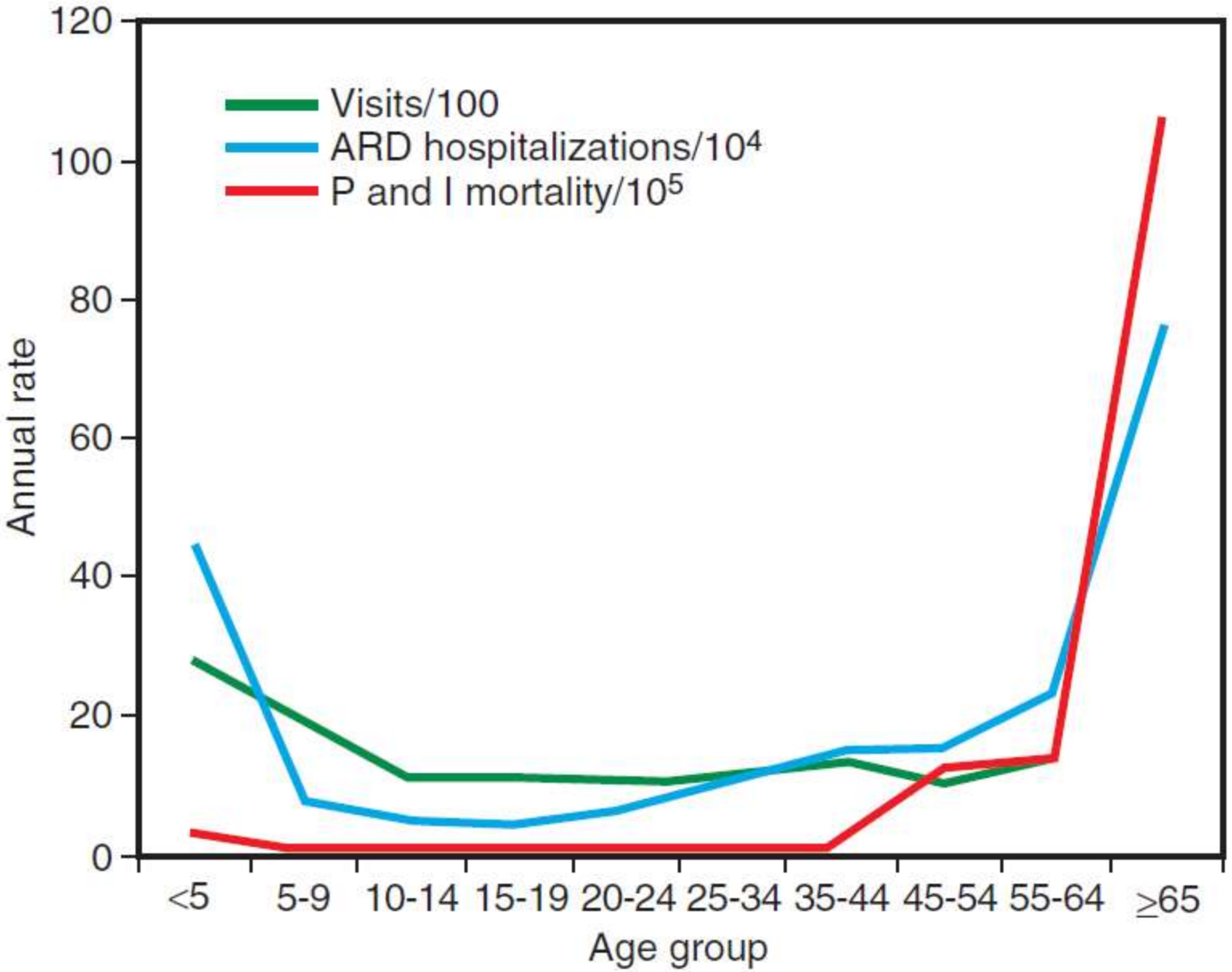


Figure 167-3. Typical epidemic curve in interpandemic era. Principles and Practices of Infectious Diseases. Mandell, Douglas, and Bennett's, 8th ed.

Most at risk for morbidity, mortality

- Mortality highest in older adults >65
- High risk medical conditions
  - Cardiovascular, pulmonary, metabolic diseases, kidney disease, hemoglobinopathies, immune defects, neurologic disease
- Nursing home residents
- Immunosuppressed/HIV infected
- 2nd and 3rd trimester pregnancy, postpartum
- Morbidly obese
- Native Americans/Alaskan natives
- Children < 2 years old

Transmission

- Person-to-person via infected respiratory secretions
- Predominantly by large particles (droplet)
- Usual reproduction number (number of secondary cases generated by one case): 1-3
- Usually a single strain causes nearly all cases during an epidemic
- Antigenic variation of HA, NA determines “shift” vs “drift”
  - New variants, little to no preexisting immunity in population

VIEWPOINTS

Observations on Mortality during the 1918 Influenza Pandemic

Jeffrey Luk,[1] Peter Gross,[1,2] and William W. Thompson[3]

[1]Department of Internal Medicine, Hackensack University Medical Center, Hackensack, and [2]New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; [3] National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta

Luk, j. et al. Clinical Infectious Diseases 33:1375-8, 2001

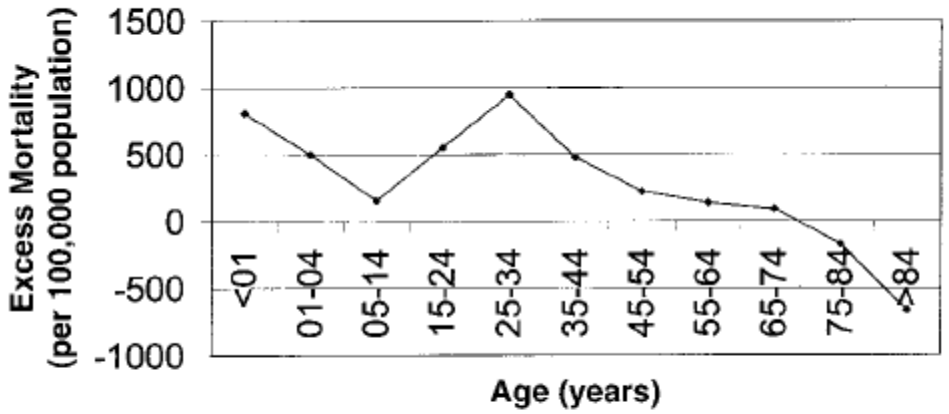


Figure 1. Age group–specific annual excess mortality due to pneumonia and influenza during the influenza pandemic in 1918. The average annual excess mortality for the period of 1913–1917 was used as the baseline.

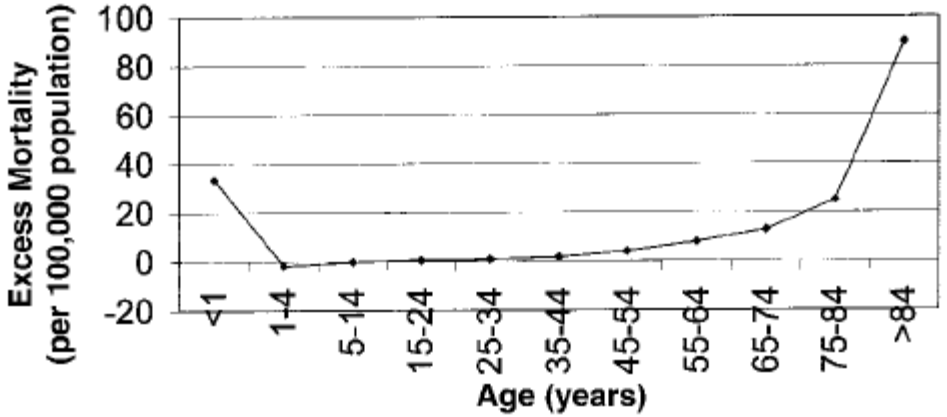


Figure 2. Age group–specific annual excess mortality due to pneumonia and influenza during the influenza pandemic in 1968. The average annual excess mortality for the period of 1963–1967 was used as the baseline.

Luk, j. et al. Clinical Infectious Diseases 33:1375-8, 2001

1918 Influenza Vulnerable Populations

- Men age 25-40 years
- South Africa:
  - Case fatality rate 5.9% nonwhites
  - 2.6% whites
  - Kimberly diamond miners 22.4%
  - Rand gold miners 1.9%
- Rhodesia 9.2% mining villages and 2.3% other villages
- New Zealand mortality rate 7x higher for indigenous Maori

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet]. 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

Bacterial Pneumonia in 1918

- <5% of deaths occurred within 3 days of illness
- Median onset of illness to death 7-10 days

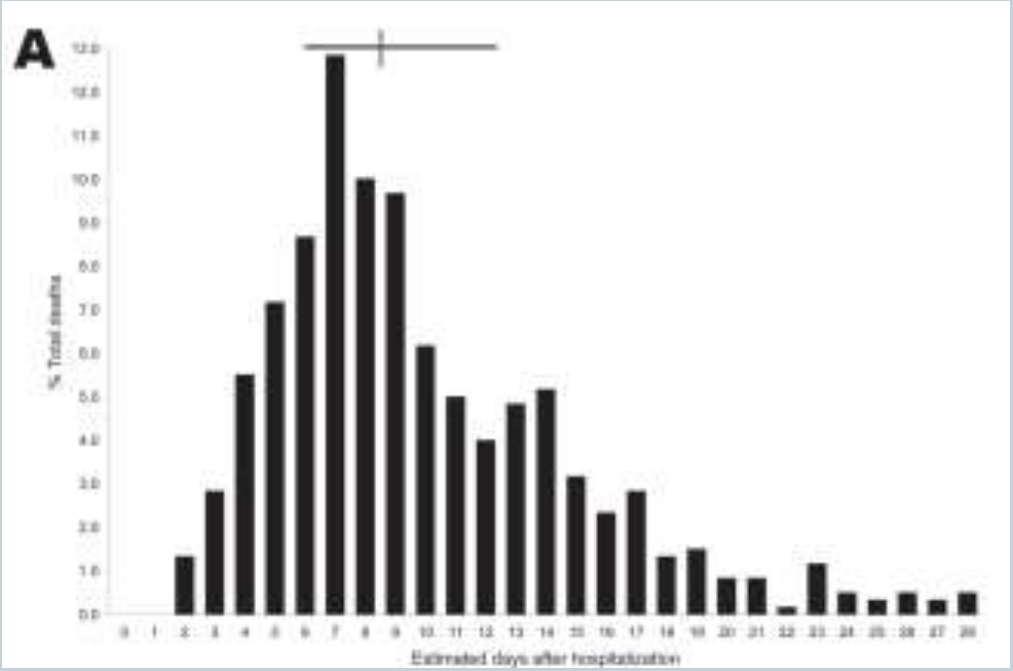


Figure 1. Percentage distributions of fatal cases of influenza–pneumonia during 1918–19 influenza pandemics, by estimated days of illness before death. A) Influenza–bronchopneumonia, Cook County Hospital, Chicago, Illinois, USA (n = 599)

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet]. 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

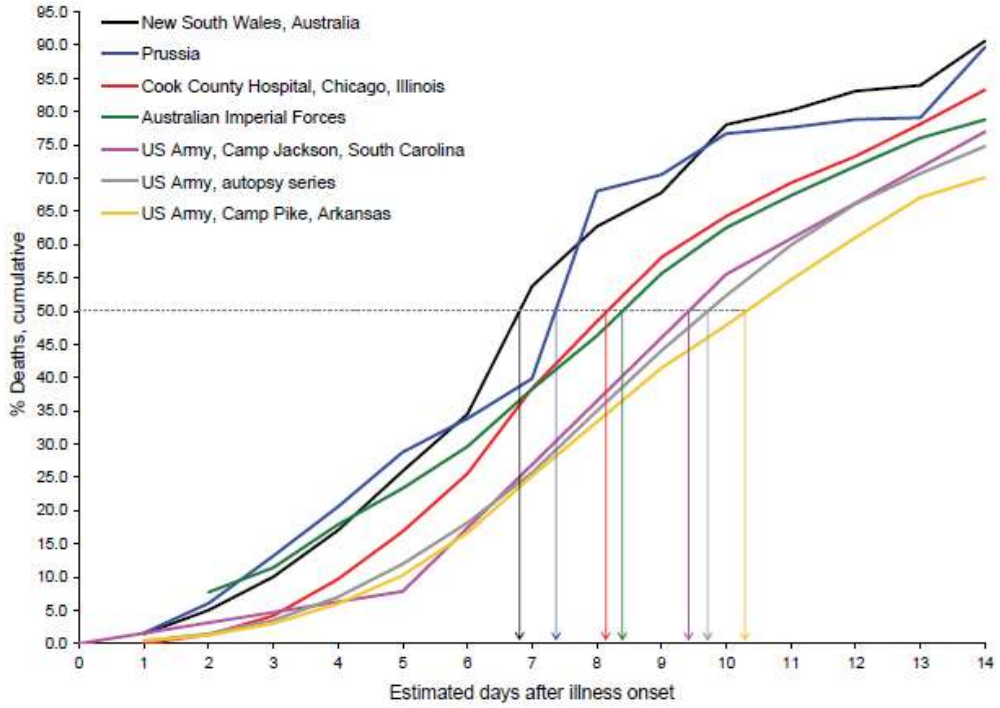


Figure 2. Cumulative percentage deaths from influenza–pneumonia, by days (estimated) from illness onset, among fatal cases during various epidemics, 1918–19 (*5,17–22*). Vertical arrows indicate median no. days to death.

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet], 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

Predominant Pneumonia at Army Camps, Fall 1918

- Haemophilus influenza 6 camps
- Streptococcus pneumonia 12 camps
- S. pyogenes 3 camps
- Staphylococcus aureus 3 camps

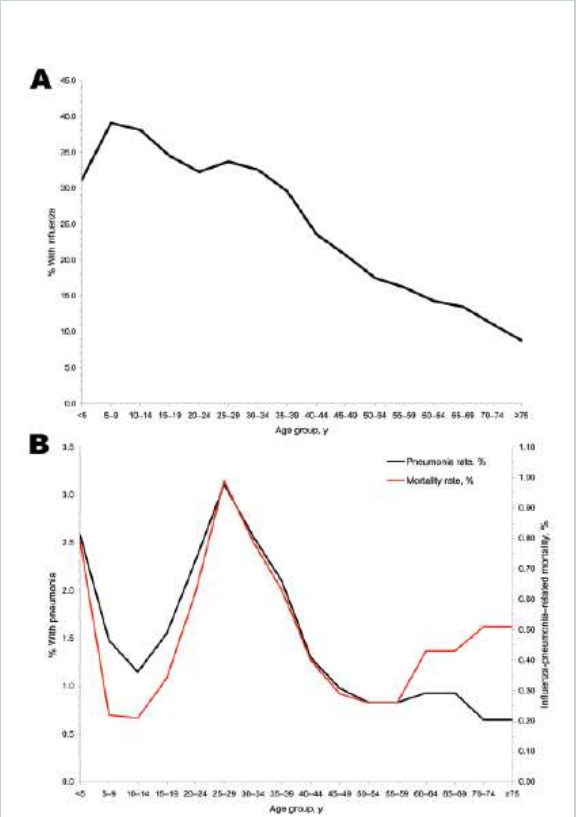


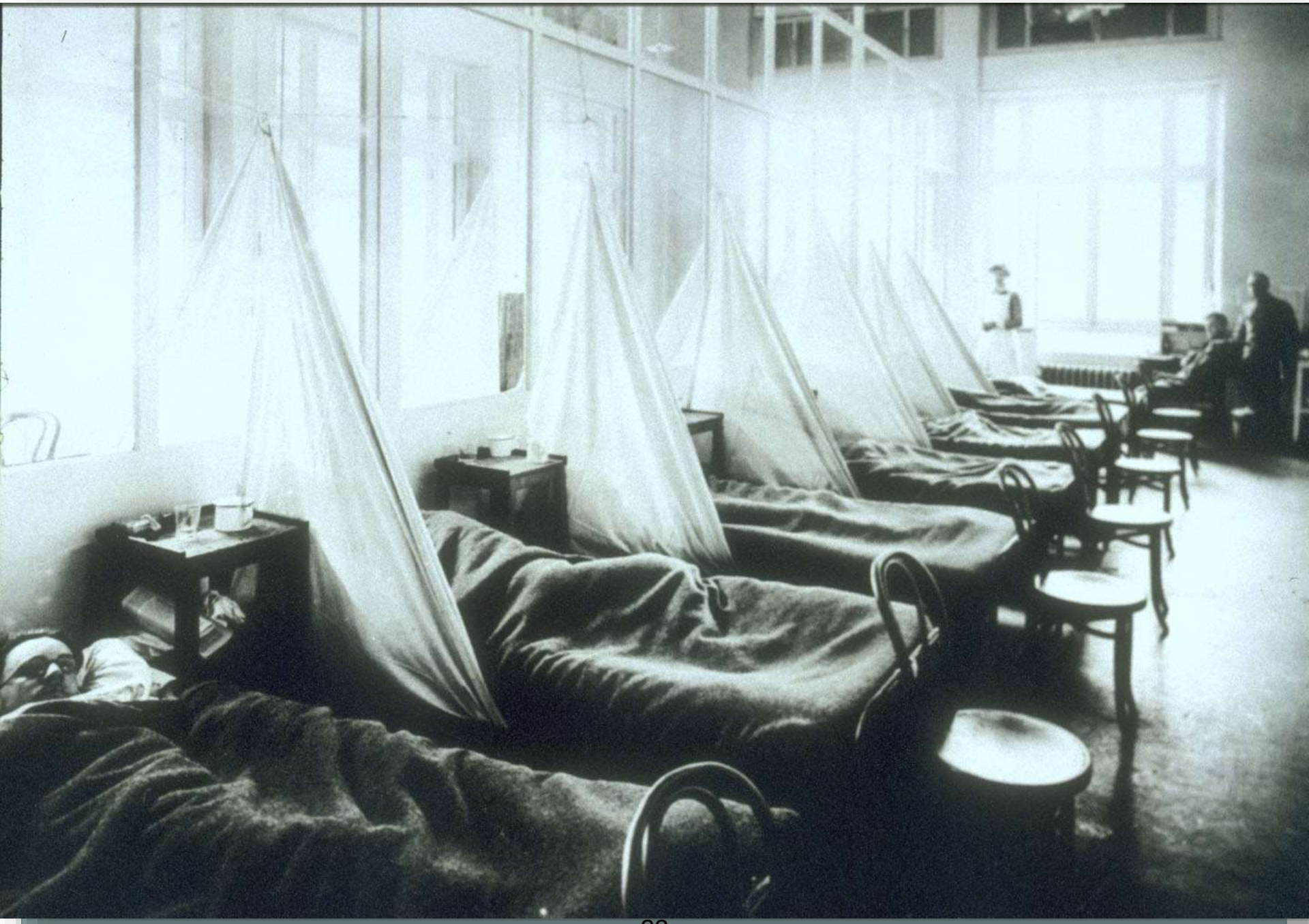
Figure 5. A) Estimated age group–specific influenza case rates (*15,16*). B) Estimated age group–specific pneumonia rates and mortality rates, based on household surveys of 10 communities throughout the United States (*15,16*).

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet]. 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

Camp Devens, Mass.Surgical Ward No 16 29 September 1918 (Base Hospital)

"…These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hospital they very rapidly develop the most viscous type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up…"

http://virus.stanford.edu/uda/



1918 Bacterial Pneumonia Theory

- Virus induced prolonged production of interferons and proinflammatory cytokines destroys respiratory epithelium, alters physical and immune defenses of lower respiratory tract
- Invasion of lungs by bacteria
- Some infected individuals , esp. in crowded spaces, become “cloud adults” or “super-spreaders”

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet]. 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

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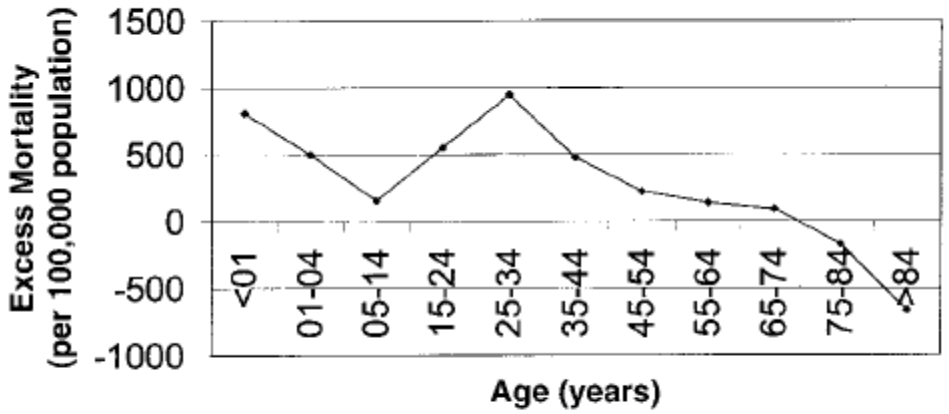

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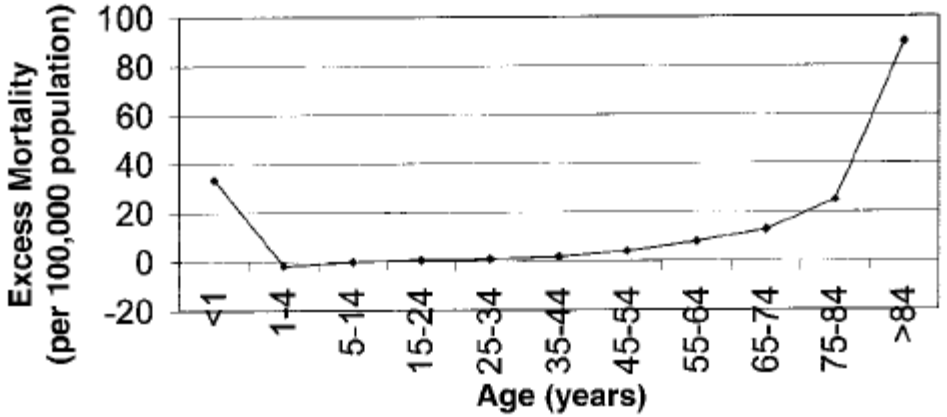

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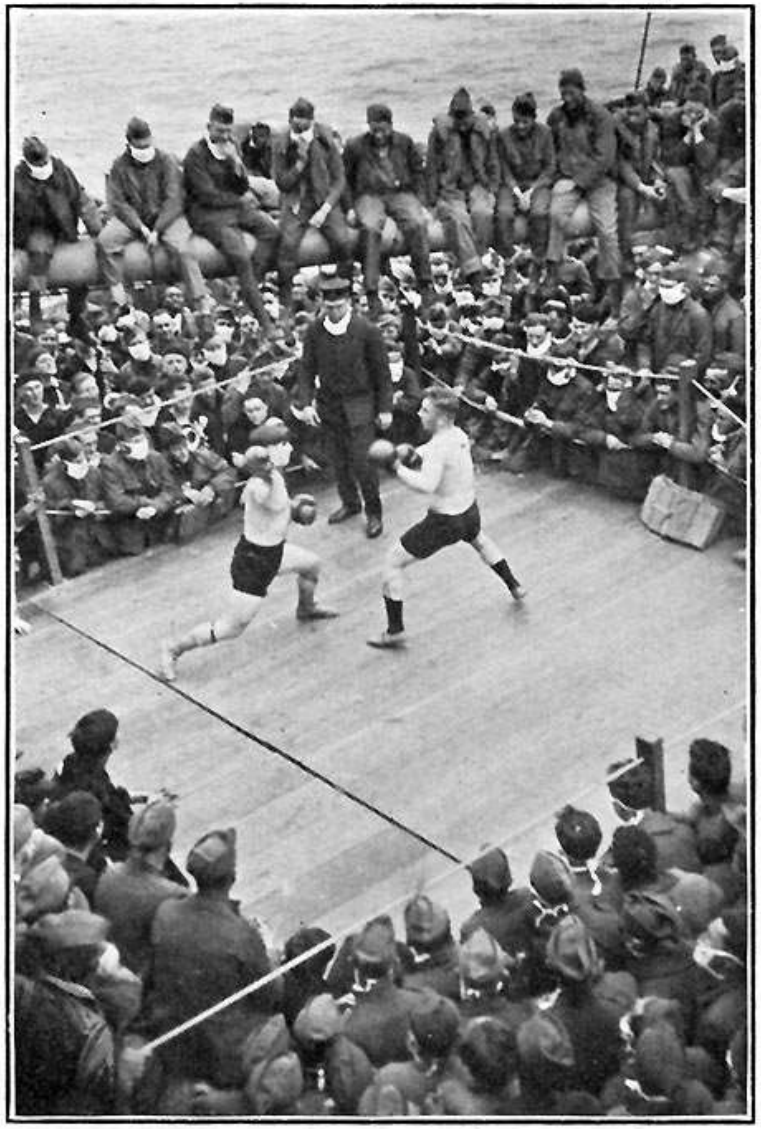
Luk, j. et al. Clinical Infectious Diseases 33:1375-8, 2001

Photo # NH 2654 Crowded extemporized sleeping area in Drill Hall at Naval Training Station, San Francisco

http://www.history.navy.mil/photos/events/ev-1910s/ev-1918/influenz.htm

Photo # NH 103264 Boxing match on USS Siboney



Boxing Bout on Fo'c'le
"Influenza Masks in Use"

http://www.history.navy.mil/photos/events/ev-1910s/ev-1918/influenz.htm

"The 1918 Influenza Pandemic: Insights for the 21st Century"

- Where did the 1918 virus originate?
  - Unknown; unlike H5N1, from an avian influenza lineage genetically distinct from those currently known
- What was the pathogenesis, and why did so many people die?
  - Different pathogenesis in 1918 not documented:
    - Causes of death in 1918 similar to those during other pandemics
    - Most fatalities had secondary pneumonias caused by common bacteria or, in a minority of cases, ARDS-like syndromes
    - Higher proportion of severe cases at all ages
    - 1918 virus-virulence determinants not yet mapped

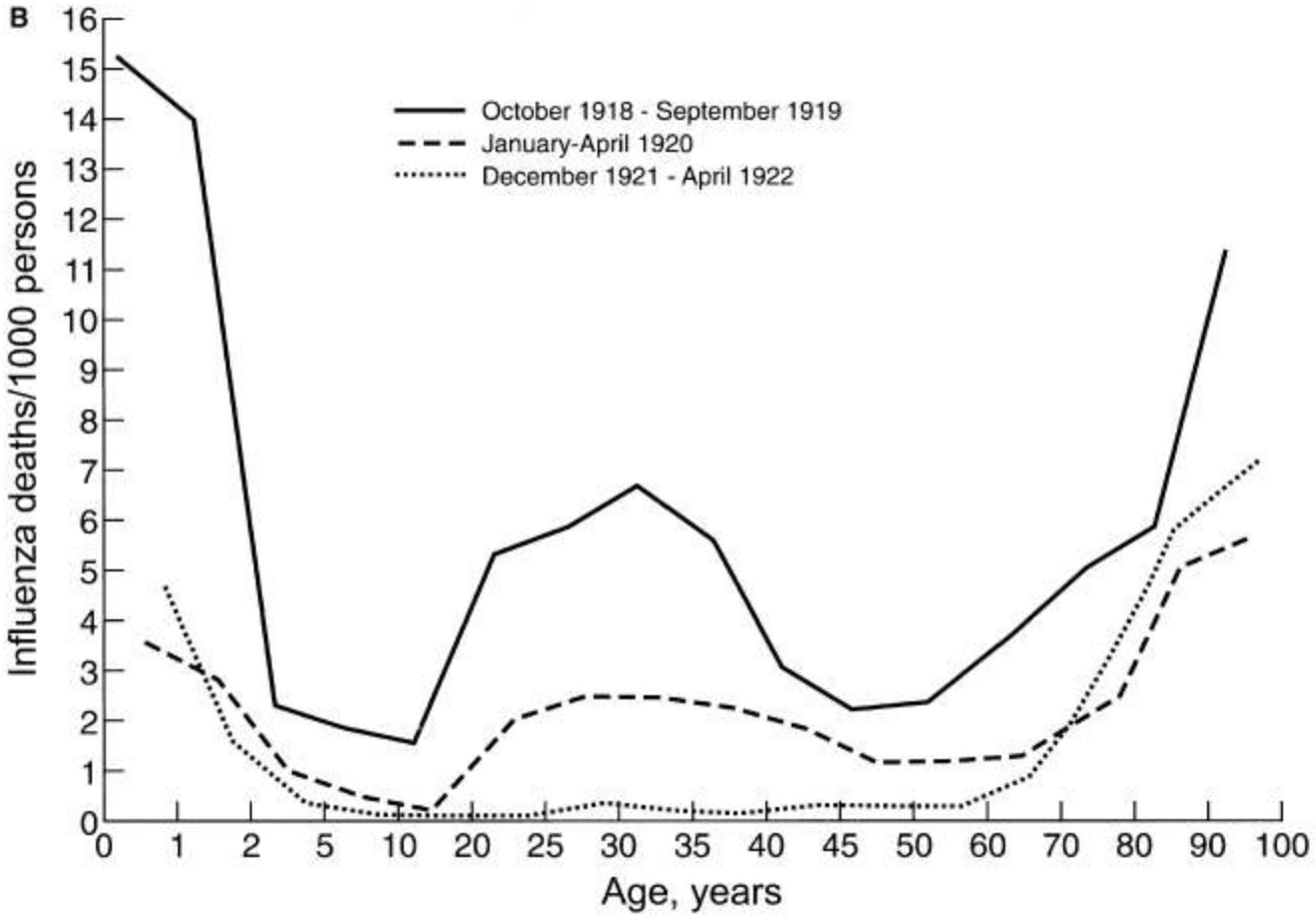
David M. Morens and Anthony S. Fauci. Clinical Infectious Diseases, 195:1018-1028, 2007

"The 1918 Influenza Pandemic: Insights for the 21st Century"

- Why were there so many deaths among the young and healthy?
  - Unknown; unappreciated host or environmental variables possible, such as robust immunological response to the virus in younger individuals, resulting in enhanced tissue damage
- Why was mortality among the elderly lower than expected?
  - Unknown; evidence is consistent with prior exposure to a virus—conceivably the virus associated with the 1847 pandemic—eliciting protective immunity
- Why were there 3 pandemic waves during 1918–1919, and what are the implications for predicting future pandemic spread?
  - Unknown; at least 2 virus variants during second wave
  - Identity of viruses during first and third waves not known
  - Epidemiology of rapidly recurrent waves not understood

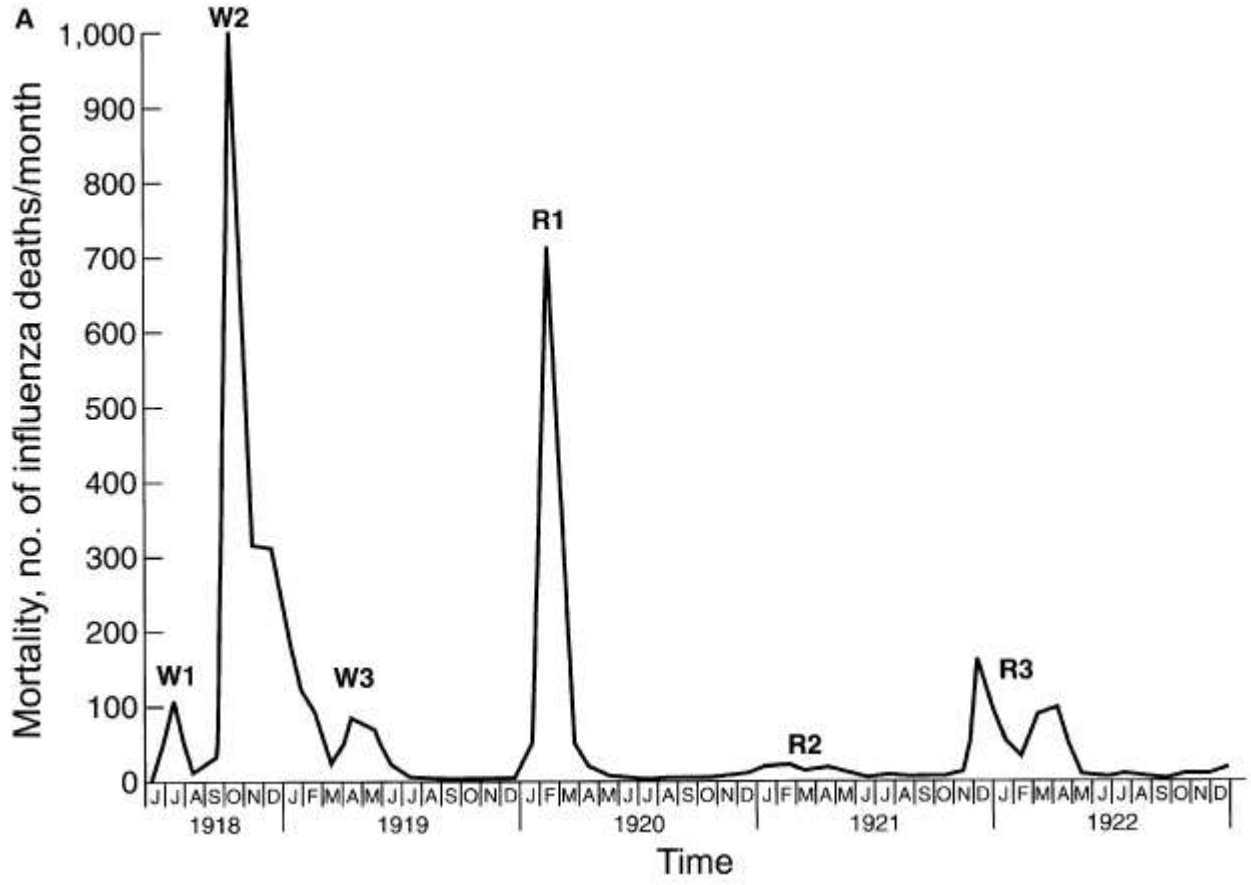
David M. Morens and Anthony S. Fauci. Clinical Infectious Diseases, 195:1018-1028, 2007

Age-specific influenza-associated mortality in Breslau, from July 1918 to April 1922.



David M. Morens and Anthony S. Fauci. Clinical Infectious Diseases, 195:1018-1028, 2007

Monthly influenza-associated mortality in Breslau, Silesia (now Wroclaw, Poland), from June 1918 through December 1922



David M. Morens and Anthony S. Fauci. Clinical Infectious Diseases, 195:1018-1028, 2007

"The 1918 Influenza Pandemic: Insights for the 21st Century"

- Do influenza pandemics occur in predictable cycles?
  - Insufficient evidence for pandemic cyclicity
  - Steps in pandemic emergence not fully understood
- Are we better able to prevent morbidity and mortality today?
  - Yes, in developed world with advanced medical care, antibiotics, antivirals, and effective public health
  - Preventive vaccines would be critical if available in time
  - However, developing world still at great risk

David M. Morens and Anthony S. Fauci. Clinical Infectious Diseases, 195:1018-1028, 2007

SUPPLEMENT ARTICLE

Lessons Learned from Reconstructing the 1918 Influenza Pandemic

Adolfo García-Sastre[1] and Richard J. Whitley[2]

[1]Department of Microbiology, Mount Sinai School of Medicine, New York, New York; [2]Departments of Pediatrics, Microbiology, Medicine, and Neurosurgery and Center for Biodefense and Emerging Infections, University of Alabama at Birmingham, Birmingham

HA Gene

- Receptor binding glycoprotein, responsible for mediating fusion with host endosomal membrane
- Must be activated by host protease (trypsin)
- Highly pathogenic avian viruses have multibasic cleavage site recognized by ubiquitous proteases
  - 1918 strain does not have this
- Yet 1918 HA essential for high virulence in mouse and egg pathogenicity models

HA Gene

- HA of human flu binds to α2,6 sialic acids
- Avian viruses bind α2,3 linked sialic acids
- 1918 HA differs only at aa 225
  - 225 glutamic acid: human binding
  - 225 glycine: dual specificity binding both human and avian receptors
- Also, single aa change at 190 switches receptor binding from human to avian
- Thus single point mutations can switch receptor specificity

Origin of 1918 Influenza

JOURNAL OF VIROLOGY, Aug. 2002, p. 7860–7862 Vol. 76, No. 15
0022-538X/02/$04.00+0 DOI: 10.1128/JVI.76.15.7860–7862.2002

1917 Avian Influenza Virus Sequences Suggest that the 1918 Pandemic Virus Did Not Acquire Its Hemagglutinin Directly from Birds

Thomas G. Fanning,[1]* Richard D. Slemons,[2] Ann H. Reid,[1] Thomas A. Janczewski,[1] James Dean,[3] and Jeffery K. Taubenberger[1]

Division of Molecular Pathology, Department of Cellular Pathology and Genetics, Armed Forces Institute of Pathology, Rockville, Maryland 20850-3125[1]; Department of Veterinary Preventive Medicine, College of Veterinary Medicine, Ohio State University, Columbus, Ohio 43210[2]; and Division of Birds, National Museum of Natural History, Washington, D.C. 20560[3]

Received 29 January 2002/Accepted 25 April 2002

1957-58 Influenza Pandemic

Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science
Volume 7, Number 3, 2009 © Mary Ann Liebert, Inc.
DOI: 10.1089/bsp.2009.0729

Public Health and Medical Responses to the 1957-58 Influenza Pandemic

D. A. Henderson, Brooke Courtney, Thomas V. Inglesby, Eric Toner, and Jennifer B. Nuzzo

- September opening of schools a major factor in initiating outbreak
- No school closings, but games canceled due to ill players

Henderson, DA et al, Biosecurity and Bioterrorism: Biodefense strategy, Practice and Science. 7:1-9, 2009

1957-58 Influenza Pandemic

- Large number of non flu excess deaths
- Vaccine arrived at the end of outbreak, 60% effective, sufficient for 17% population
- GDP decrease only 1%

Table 1. Mortality Characteristics of Type A Influenza Epidemics, United States, 1937-1963[a]

	Number of Excess Deaths	
Period of Excess Mortality	*Pneumonia and Influenza*	*All Causes*
Dec 1934-Jan 1935	5,800	11,000
Jan-Mar 1937	29,000	46,000
Mar 1939	3,100	6,100
Dec 1940-Feb 1941	7,200	16,000
Dec 1943-Jan 1944	21,000	53,000
Mar-Apr 1947	4,800	13,000
Mar-Apr 1950	3,200	11,000
Feb-Apr 1951	4,000	15,000
Jan-Mar 1953	10,000	30,000
Oct 1957-Mar 1958	**19,000**	**62,000**
Mar-Apr 1959	1,500	4,100
Jan-Mar 1960	12,000	27,000
Feb-Apr 1963	12,100	57,000

Henderson, DA et al, Biosecurity and Bioterrorism: Biodefense strategy, Practice and Science. 7:1-9, 2009

1977 H1N1 Reemergence in Humans

VIROLOGY 89, 613–617 (1978)

Genetic Relatedness between the New 1977 Epidemic Strains (H1N1) of Influenza and Human Influenza Strains Isolated between 1947 and 1957 (H1N1)

C. SCHOLTISSEK,[1] V. VON HOYNINGEN, AND R. ROTT

Institut für Virologie, Justus-Liebig-Universität Giessen, Giessen, Germany

Accepted May 19, 1978

- May 1977 outbreaks in Tientsin, China
- November 1977 Soviet Union, Hong Kong
- Virus A/USSR/77 reestablished H1N1

Scholtissek, C et al. Virology 89:613-617, 1978

1977 H1N1 Reemergence in Humans

VIROLOGY 89, 632–636 (1978)

Antigenic Similarity of Influenza A (H1N1) Viruses from Epidemics in 1977–1978 to "Scandinavian" Strains Isolated in Epidemics of 1950–1951

ALAN P. KENDAL,* GARY R. NOBLE,* JOHN J. SKEHEL,† AND WALTER R. DOWDLE*

* *WHO Collaborating Center for Influenza, Center for Disease Control, U.S. Public Health Service, Atlanta, Georgia 30333 and †WHO Collaborating Center for Influenza, National Institute for Medical Research, Mill Hill, London, England*

Accepted May 19, 1978

Kendal, AP. Virology 89:632-636, 1978

1977 H1N1 Reemergence in Humans

- H1N1 did not circulate from 1957-1977
- Nov 1977 H1N1 strain appeared in former Soviet Union, Hong Kong and China
- Affected primarily young people, mild presentation
- Genetics of virus very close to 1950 strain, but different from 1947 and 1957, suggesting that the outbreak strain had been preserved from 1950

[1]Zimmer, SM and Burke, DM. New England J. Medicine 361:279-285, 2009
[2] Palese, P. Nature medicine 12:S82-S87, 2004

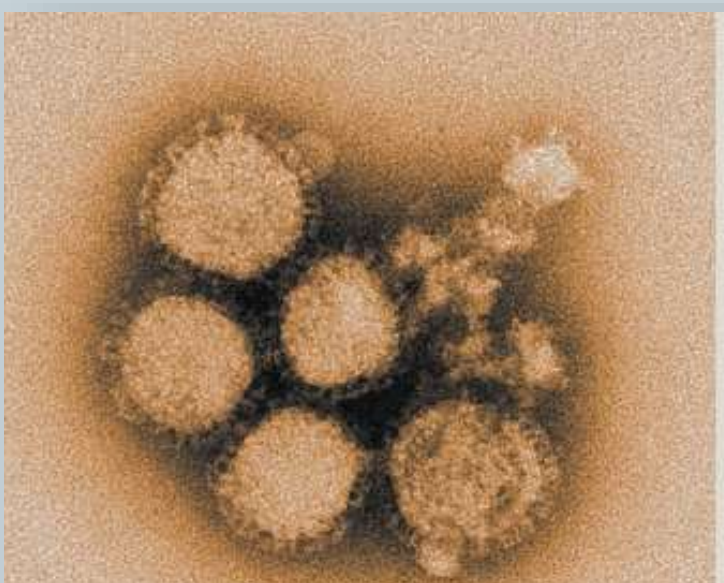
H1N1 Reemergence in Humans

- "The reemergence was probably an accidental release from a laboratory source in the setting of waning population immunity to H1 and N1 antigens"[1]
- "Although there is no hard evidence available, the introduction of this 1977 H1N1virus is now thought to be the result of vaccine trials in the Far East involving the challenge of several thousand military recruits with liveH1N1 virus"[2]

[1]Zimmer, SM and Burke, DM. New England J. Medicine 361:279-285, 2009

[2] Palese, P. Nature medicine 12:S82-S87, 2004

Virus of the Year
Science, 2009



Near miss. The H1N1 virus was less virulent than feared, but the next pandemic could be worse.

SPECIALSECTION

VIRUS OF THE YEAR

THE NOVEL H1N1 INFLUENZA

FOR YEARS, SCIENTISTS HAVE BEEN WARNING THAT an influenza pandemic could strike at any moment, triggering a global catastrophe on the order of the 1918 Spanish flu. They imagined the culprit would surface in Asia—and, since 2003, have worried that the avian influenza strain H5N1 might be it. Health officials worldwide drafted one preparedness plan after another.

Enserink and Cohen, Science 326:1607, 2010

Virus of the Year
Science, 2009

- Epidemic began in North America, not Asia
- Originating swine virus already circulating in humans (and not H5N1)
- Dangerous in young and pregnant, otherwise mild
- Discovered early in humans
  - Mexico open with epidemiology, aggressive with intervention
- New vaccines and drugs approved quickly
- Good information flow over the internet

Enserink and Cohen, Science 326:1607, 2010

Virus of the Year
Science, 2009

- Poor flu surveillance in pigs, virus undetected for years, circulates for months in humans before detection (too late for quarantine)
- Travel bans and human quarantines against the advice of WHO
- Egypt kills all pigs despite no pig to human transmission found
- Vaccines hit snags
- Poor countries were last in line for vaccines

Enserink and Cohen, Science 326:1607, 2010

Virus of the Year
Science, 2009

- US did not use vaccine adjuvants to stretch vaccine supplies
- European countries used adjuvants, but insisted on 2 dose regimen despite evidence that 1 dose was protective
- Rumors and mistrust of vaccine high
  - Denounced by celebrities
  - “it hasn’t been tested on humans”
  - “ it’s a WHO-led plot to depopulate the world”

Enserink and Cohen, Science 326:1607, 2010

MAJOR ARTICLE

Initial Response of Health Care Institutions to Emergence of H1N1 Influenza: Experiences, Obstacles, and Perceived Future Needs

Ebbing Lautenbach,[1,2,3,4] Sanjay Saint,[5] David K. Henderson,[6] and Anthony D. Harris[7,8]

[1]Division of Infectious Diseases, Department of Medicine, [2]Department of Biostatistics and Epidemiology, [3]Center for Clinical Epidemiology and Biostatistics, and [4]Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [5]Ann Arbor VA Medical Center and Department of Internal Medicine, University of Michigan, Ann Arbor; [6]Hospital Epidemiology Service, and Office of the Director, Clinical Center, National Institutes of Health, Bethesda, [7]Department of Epidemiology and Preventive Medicine, [8]VA Maryland Healthcare System, University of Maryland, Baltimore, Maryland

(See the editorial commentary by Carlson and Perl, on pages 528–30.)

Survey of healthcare epidemiologists regarding the H1N1 outbreak

- 77.7% agreed with mandatory vaccination
- Problems to address:
- Widespread hoarding of antiviral medicines
- Neglect of other infection prevention programs as attention diverted to H1N1
- Better availability of resources and personnel to prevent “burnout”

Lautenbach, E et al. Clinical infectious diseases 50:523-7, 2010

“The most difficult challenge…”

“The most difficult challenge would probably not be to increase medical knowledge about treatment and prevention but to increase medical capacity and resource availability (e.g., hospital beds, medical personnel, drugs, and supplies) and public-health and community-crisis responses to an event in which 25–50% of the population could fall ill during a few weeks’ time. Health-care systems could be rapidly overwhelmed by the sheer volume of cases; ensuring production and delivery of sufficient quantities of antivirals, vaccines, and antibiotics, as well as providing widespread access to medications and medical care, particularly in impoverished regions, would be a sobering challenge.”

David M. Morens and Anthony S. Fauci. The 1918 Influenza Pandemic: Insights for the 21st Century. Clinical Infectious Diseases, 195:1018-1028, 2007

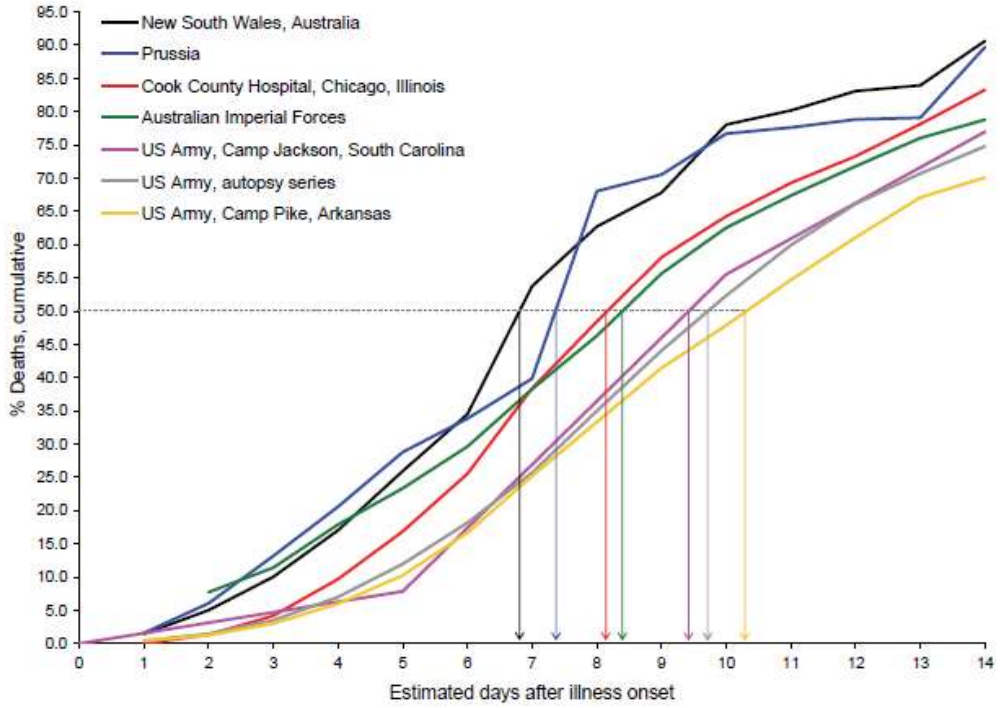


Figure 2. Cumulative percentage deaths from influenza–pneumonia, by days (estimated) from illness onset, among fatal cases during various epidemics, 1918–19 (*5,17–22*). Vertical arrows indicate median no. days to death.

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet], 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

Predominant Pneumonia at Army Camps, Fall 1918

- Haemophilus influenza 6 camps
- Streptococcus pneumonia 12 camps
- S. pyogenes 3 camps
- Staphylococcus aureus 3 camps

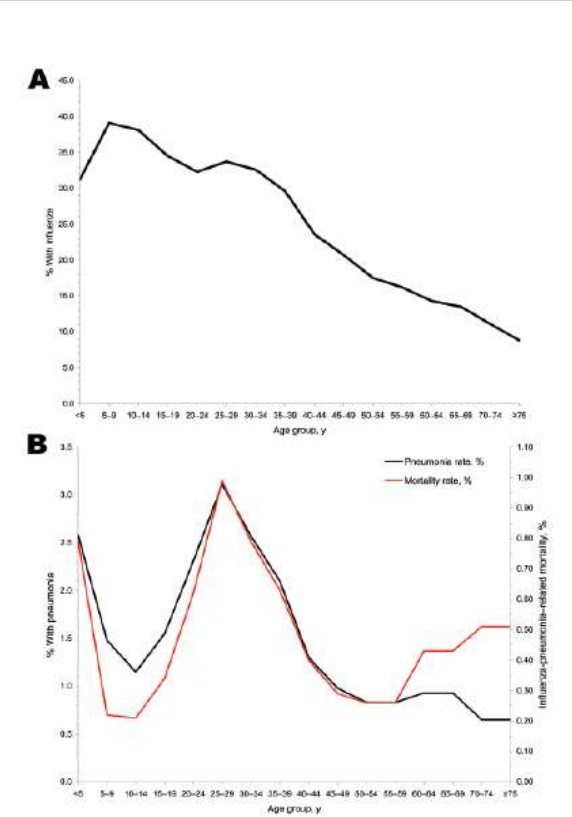


Figure 5. A) Estimated age group–specific influenza case rates (*15,16*). B) Estimated age group–specific pneumonia rates and mortality rates, based on household surveys of 10 communities throughout the United States (*15,16*).

Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis [serial on the Internet]. 2008 Aug [*22 FEB 2010*]. Available from http://www.cdc.gov/EID/content/14/8/1193.htm

Camp Devens, Mass.Surgical Ward No 16 29 September 1918 (Base Hospital)

"…These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hospital they very rapidly develop the most viscous type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up…"

http://virus.stanford.edu/uda/

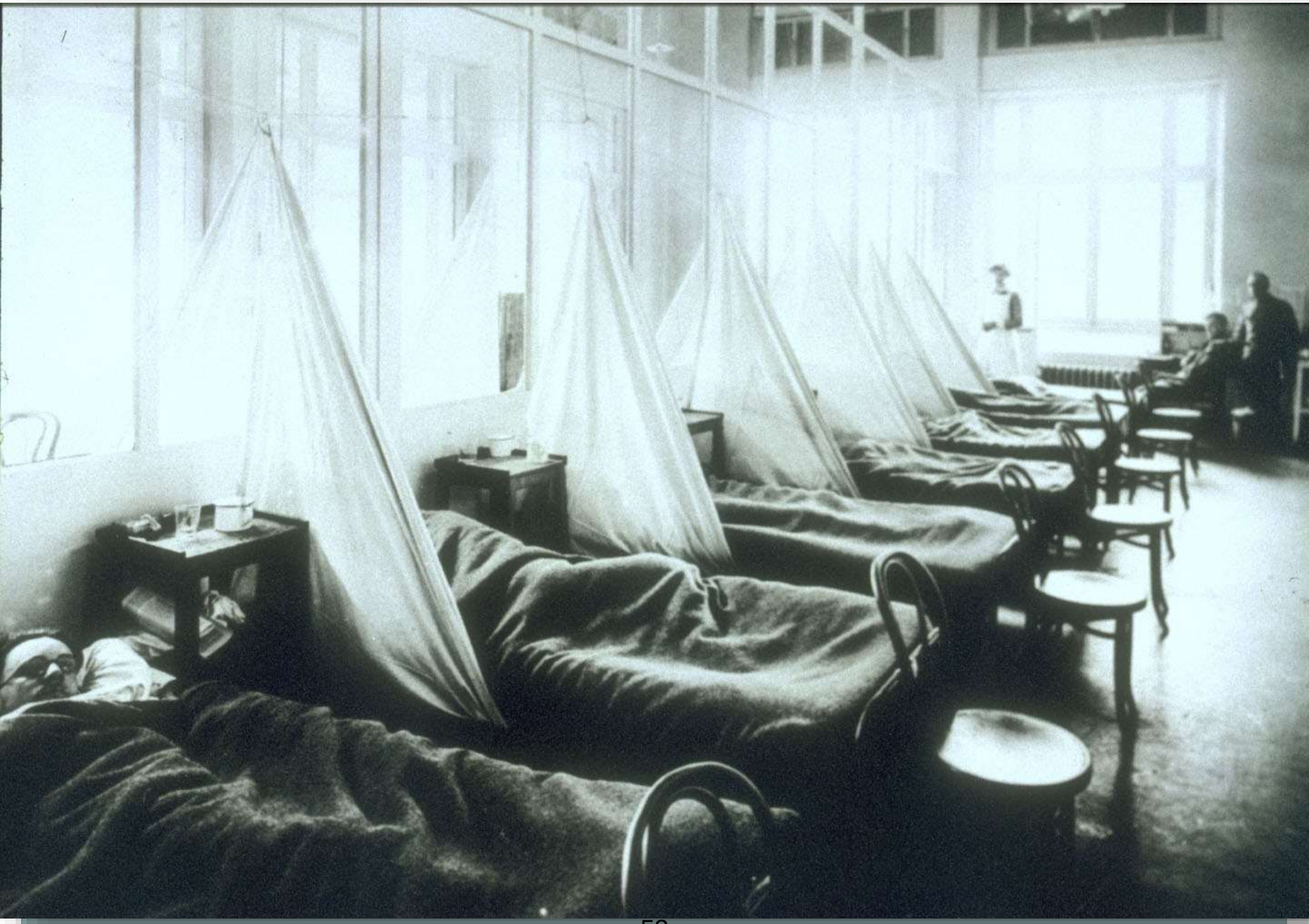


Fig. 1-20. Sleeping quarters for basic recruits in 1962. Notice the staggering of head and feet (by pillow placement) to help prevent the spread of airborne disease.
Photograph: Courtesy of the 37th Training Wing Historian's Office, Lackland Air Force Base, San Antonio, Texas.


EXIT

Increased vulnerability

- Crowding
- Environmental exposures
- Constant introduction of immunologic naives
- Emotional stress
- Increased exertion
- Extremes of temperature
- Decreased hygiene
- Disincentives for seeking care

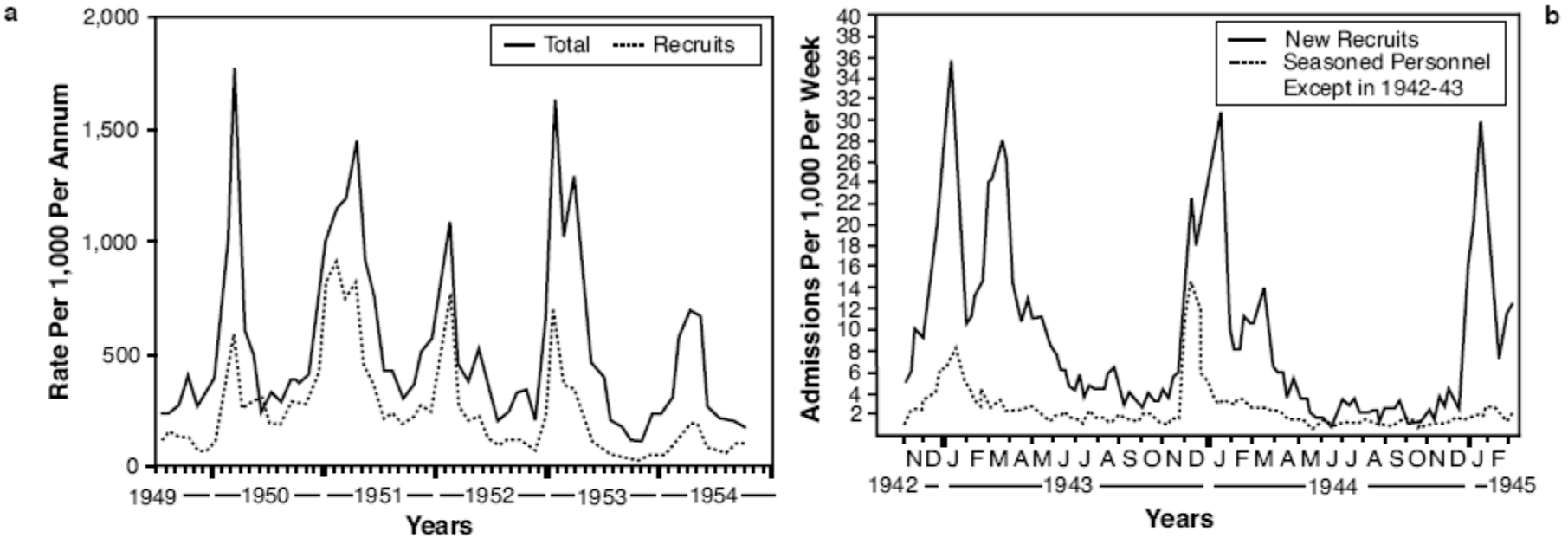
- Increased susceptibility as well as differences in presentation

Respiratory infection:

- Definitions:
- Acute Respiratory Disease (ARD) = Febrile Respiratory Illness (FRI)
  - Fever (≥100.5°F) plus one or more of the following: sore throat, cough, stuffy nose, runny nose, or diagnosis of pneumonia
  - (Includes limitation from duty by the examining physician for at least 8 hours)

- “During…WWII, from a mean strength of 6,076,135 there were 4,086,562 admissions for common respiratory disease recorded by the US Army. The average time lost from duty by a person admitted for treatment of common respiratory disease during this period was 6.2 days…The 4,086,562 cases admitted during the war period thus resulted in approximately 26.5 million man-days lost from duty, or approximately 18,000 each day of the war. An Army division is composed of 15,000 personnel. Thus, more than equivalent strength of one Army division were absent from duty every day of the war because of the common respiratory diseases.”
- -Duff FL, Thesis, Johns Hopkins University, 1952

1942: recruits vs. non-recruits' FRI



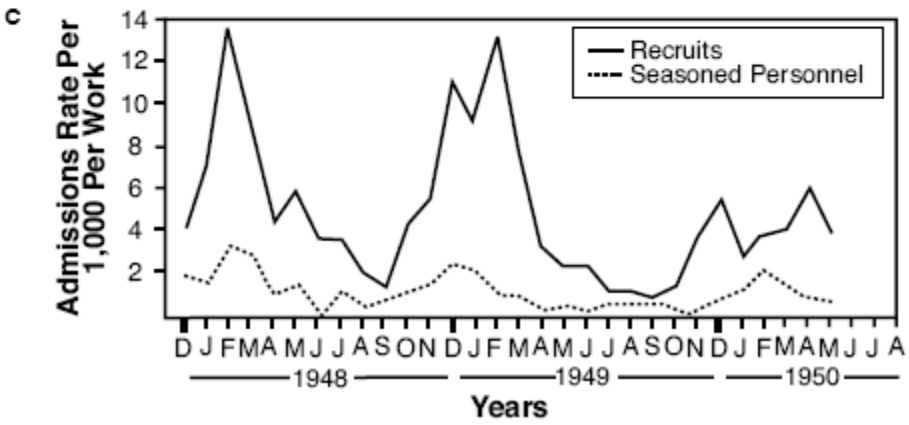


Fig. 13-1. Comparison of respiratory illness rates among recruits as compared to non-recruit ("seasoned") military populations.

a. Naval Training Center, Great Lakes, Ill, 1949 to 1954. Adapted from Seal JR. Acute respiratory diseases in recruit training stations; etiology, prevention, and control. *Mil Med.* 1955;116(4):267.

b. Fort Bragg, NC, October 31, 1942 to March 30, 1945. Adapted from Dingle JHA, Theodore J, Badger GF, et al. Acute respiratory disease among new recruits. *Am J Public Health.* 1946;36(5):441.

c. Adapted from Sartwell PE. Common respiratory disease in recruits. *Am J Hyg.* 1951;53(2):227.

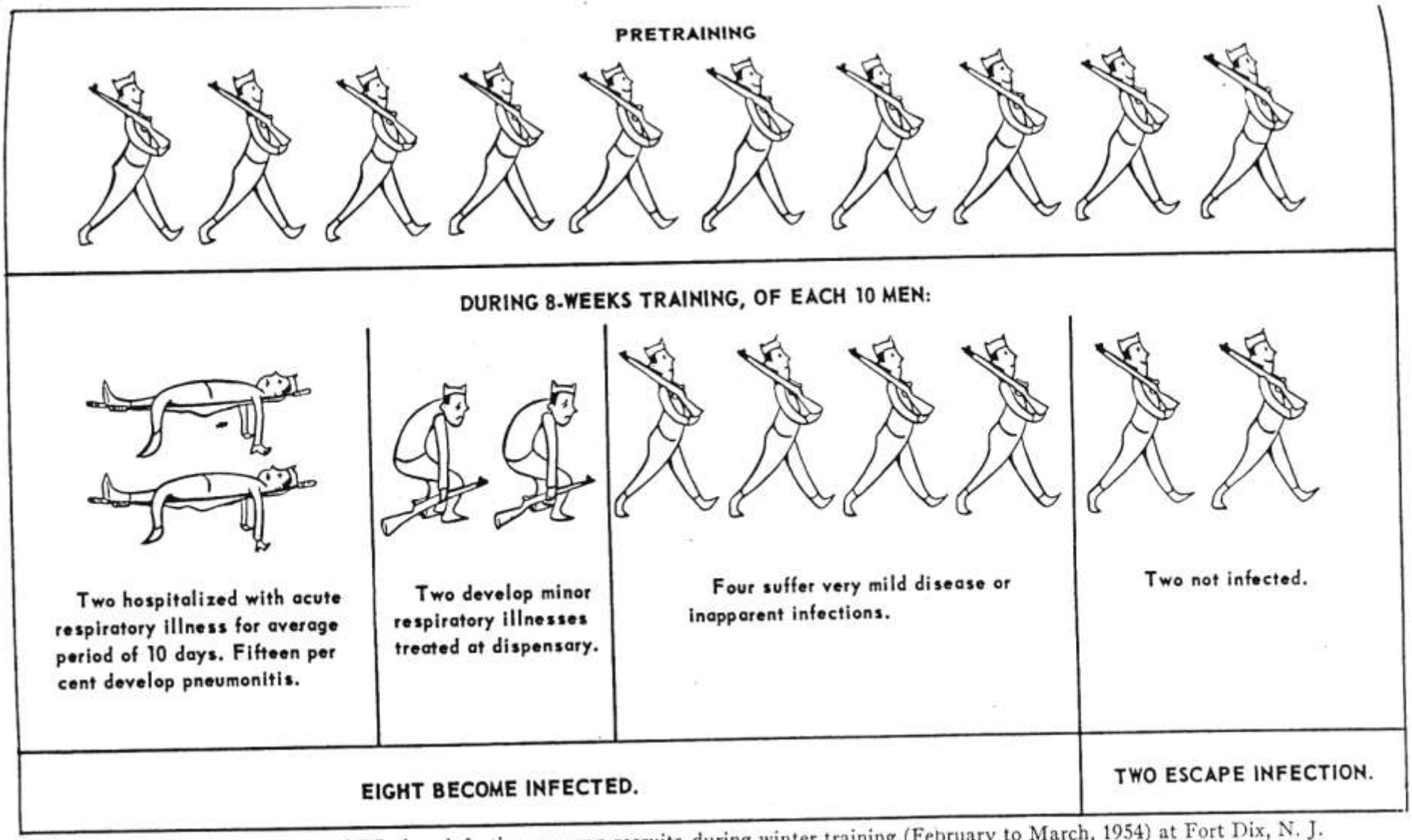
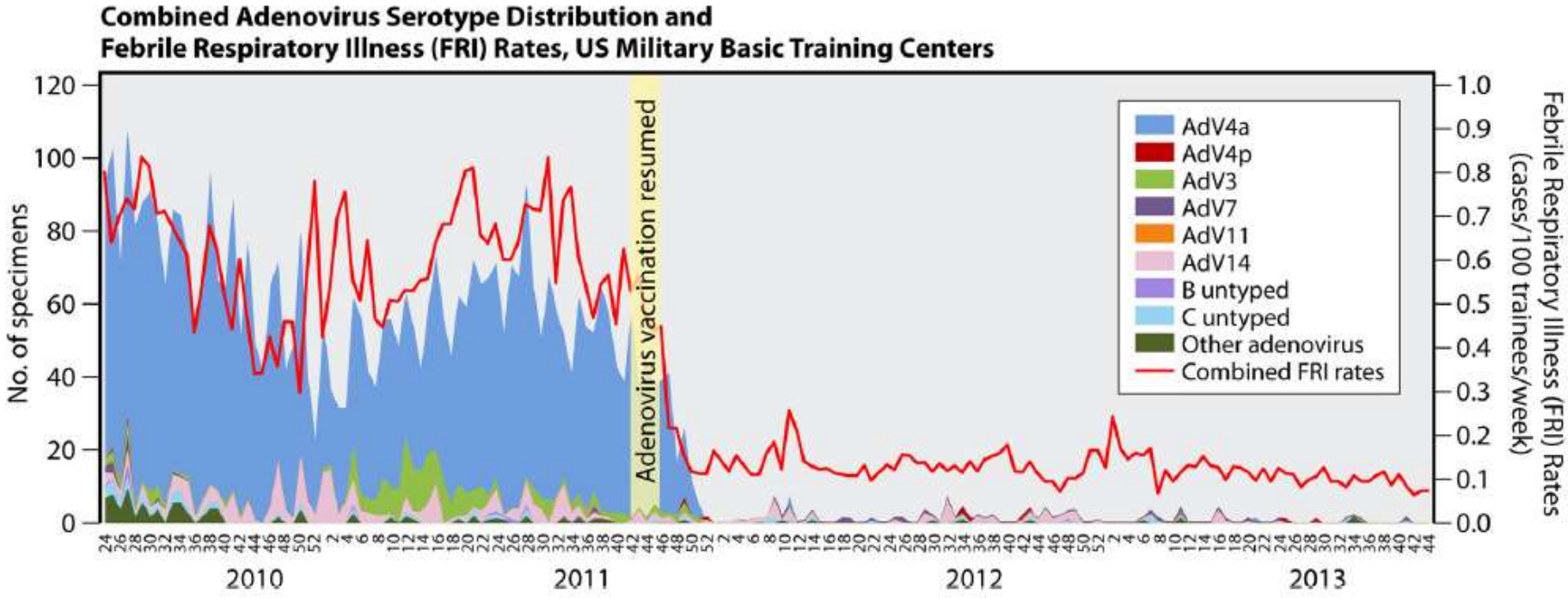


FIGURE 4. The development of RI virus infections among recruits during winter training (February to March, 1954) at Fort Dix, N. J.

Hilleman, MR Ann. NY Acad Sci 1957:67; 267



Sanchez, Clin Micro Rev 2015 (NHRC data)

Influenza A

- Important cause of FRI and pneumonia
  - Distant 2nd to adenovirus for viral FRI pathogens; generally ~10% specimen + for influenza during flu season
  - 92% vaccine effectiveness

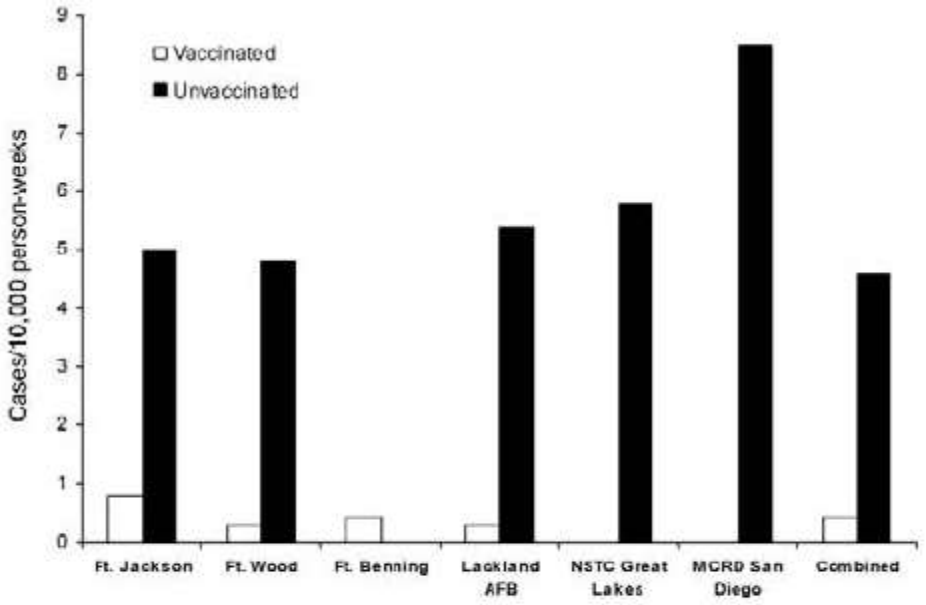


Figure. Incidence of laboratory-confirmed influenza by vaccination status. AFB, Air Force Base; NSTC, Naval Service Training Command; MCRD, Marine Corps Recruit Depot.

Strickler JK et al, Emerg Inf Dis, 2007, 13:617-19.

Influenza prevention issues

- LAIV vs TIV
  - Issues with antigen detection test
  - Inactivation of LAIV if antiviral prophylaxis required---25% of population unvaccinated at any given time assuming 14 d to immunity
- At JBSA-Lackland TIV preferred
- Directly observed therapy preferred for prophylaxis given 30-50% adherence

Other causes of FRI/ARD

- Rhinovirus
- *Bordetella pertussis*
- *Mycoplasma pneumoniae*
  - ~ 10% of CAP, year round, 6% seroconversion
- *Chlamydia pneumoniae*
  - Also causes conjunctivitis outbreaks
- RSV
- EBV

Sanchez, Clin Micro Rev 2015

Global influenza surveillance

- World Health Organization's Global Influenza Programme
- 141 national centers in 111 countries conduct year-round surveillance
- Every spring WHO publishes recommendations for northern hemisphere
- In US, FDA then determines viruses to be used in US-licensed vaccines

US Military Surveillance

- Surveillance for Basic Military Trainees
  - Febrile Respiratory Illnesses monitored & reported weekly
- Military wide
  - Influenza and influenza like illnesses are monitored worldwide
  - Specimens of interest sent to one of three centralized military laboratories (Germany, Ohio, San Antonio)
  - Weekly reports generated on rates & subtypes
  - Influenza vaccination rate tracked
- Limitation of data
  - Lag in data
  - Samples must be of interest
  - Data obtained from diagnosis codes

After vaccine strains selected:

- Private sector manufacturers begin producing vaccine
- Takes ~6 months to produce large quantities
- Manufacturers may begin to grow one or more virus strains in January for October-November delivery
- Most vaccine doses produced in chicken eggs

Immunization recommendations

- February 24, 2010
- ACIP panel voted to expand recommendation for annual influenza vaccination to all people >6 months
- Took place against incremental increases in numbers/groups recommended
- Lessons learned from pdm09(H1N1) influenza A pandemic

Antiviral medications: summary for clinicians

- Five now available in US:
  - Neuraminidase inhibitors (active against A and B): oseltamivir, zanamavir, peramivir
  - Amantidine and rimantidine (adamantanes; active against A only) not recommended

http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Why peramivir?

- Oseltamivir only available in oral formulation
- Zanamavir only available as inhaled drug, not formulated for ventilator use

- Need for parenteral neuraminidase inhibitors underscored during pandemic

2009- Emergency Use Authorization

- Use limited to hospitalized patients with lab-confirmed influenza A who did not respond to other therapy
- Randomized trial terminated early due to futility---adding peramivir to standard of care oseltamivir

Clin Infect Dis 2014, advance access Aug 12, 2014
Doi: 10.1093/cid/ciu632

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

A to Z Index

Rapivab
peramivir injection

About Rapivab | Who to Treat | Dosing and Administration | How to Order

Hor ... l & Veterinary

News

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FDA N...

FDA...

SHAR...

Now available

First-and-Only One-Dose

IV Treatment for Influenza[1]

Immediate drug delivery in your hands

For Imm... Release

Release

On December 19, the U.S. Food and Drug Administration approved Rapivab (peramivir) to treat influenza infection in adults.

- Licensed for treatment of “acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days.”

- Efficacy not established for patients with serious influenza requiring hospitalization

Peramivir---the bottom line

- Another (single dose) option for uncomplicated flu treatment
- Price is ~$950/dose vs ~$60-100 for oseltamivir
- We will know more after the next influenza pandemic

Questions?

http://www.archives.gov/exhibits/influenza-epidemic/records-list.html