…and In Flew Enza

The Never Ending Story
A History

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I have nothing to declare with respect to financial or business interests and the contents of the following presentation

Objectives

- To present a basic overview of the history of influenza disease in humans
- Discuss how the Enlightenment and the subsequent development of the scientific method affected our understanding of the influenza virus
- Review the influenza pandemics from the late 19th century to today and their impact on society

"I had a little bird.
His name was Enza.
I opened the window,
and in flew Enza."

A popular chant during the 1918 influenza epidemic

History

- Unclear as to how long influenza has circulated through human populations
  - Around 500 B.C.E.
    - Growth and urbanization of humans
      - Increasing interaction between urbanized communities
    - Hippocrates in 412 B.C.E.
    - Livy in Roman soldiers

History

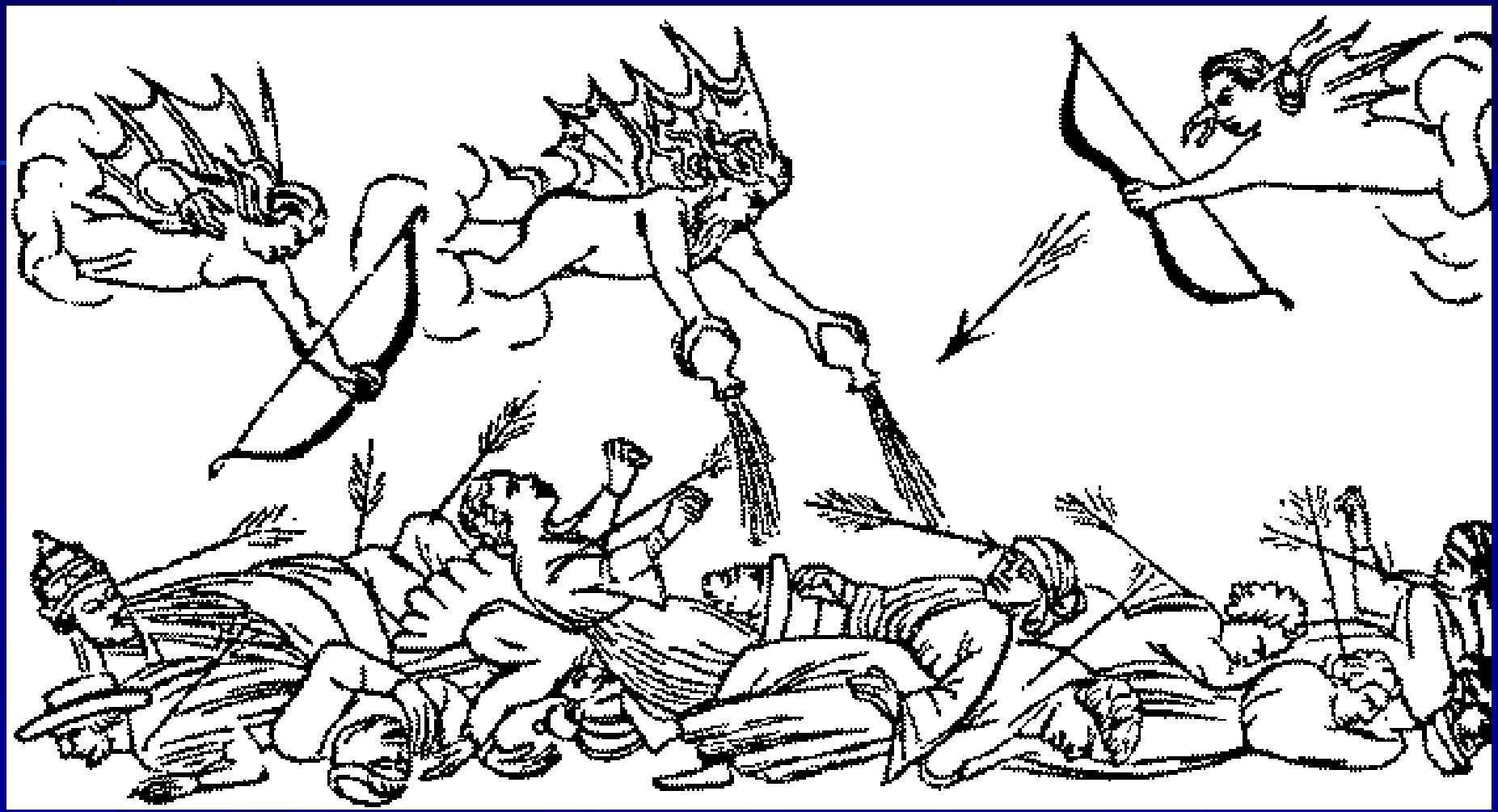
- Descriptions consistent with influenza epidemics and pandemics in Europe date back to the 16th century
  - Clinical description – fever, body aches, respiratory tract symptoms
  - Epidemiologic description in the population
    - Rapid appearance with rapid spread
    - Short duration of illness
    - Generally low mortality
      - Greatest mortality in the very young and very old
  - Rapid disapperence

"Immediately upon he Queene's arrival here, she fell acquainted with a new disease that is common in this town, called here the *Newe Acquyantance*, which passed also through her whole Courte, neither sparing lordes, ladies or damoysells, not so much as Frenche or English. It is a plague in their heads that have vt with a great cough that remanyeth with some longer, with others shorter tyme as vt findeth apte bodies for the nature of the disease. The Queene kept her bed six days. There was no appearance of danger, nor manie that die of the disease, excepte some olde folks."

Written is a letter in 1562 by Sir Thomas Randolph, ambassador from Queen Elizabeth I to the court of Mary, Queen of Scots, Edinburgh, to Cecil in London

History

- Thought of as a rather mild affliction with respect to prevailing infections of the time
  - Plague, typhus, typhoid fever, smallpox, etc.
    - 16th century
      - " the new acquaintance", " the gentle correction"
    - 17th century
      - "the new delight", "the jolly rant"
    - France – "la grippe"
    - "Influenza"
      - Italian orgin with the epidemic of 1782
        - Baleful "influence" of the stars



18th and 19th Century

- The Enlightenment
  - Scientific observation increasingly replaces supernatural explanations of disease and epidemics
- Contagionists
  - Epidemic disease transmitted through populations by infected individuals
    - Mechanism of transmission remained a mystery
    - Smallpox
- Environmentalists (miasmists)
  - Environmental sources of affliction
    - Filth, heat, moisture
    - Malaria (derived from Italian *mala aria*, bad air), yellow fever

18th and 19th Century

- The sanitary movement
  - Environmental interventions to disrupt transmission of disease
    - Cleanup of fetid pools of waste, refuse, and animal carcasses from city streets
    - Construction and maintenance of comprehensive sewage systems
- Recognition that contagion does not recognize borders
  - Cholera pandemics of 1832, 1848, and 1866
  - Convening of the First International Sanitatary Conference in 1851 in Paris
    - Eleven European countries and the Ottoman Empire
    - Five more international conferences held in the next 3 decades
      - Forerunners of the League of Nations Health Organization (LNHO) and World Health Organization (WHO)

The Dawning of Epidemiology

- Nineteenth Century - London
  - Registrar - Generals Office-1836
    - William Farr
    - national center for health statistics
    - mortality surveillance
      - Excess burials (deaths) vs expected burials
        - Quantifiable identification of epidemics
        - Taken in conjunction with contemporary accounts allow retrospective identification of epidemics and pandemics
        - 1847 – 1848 influenza epidemic

Louis Pasteur 1822 - 1895

Robert Koch
1843 - 1910

Development and Acceptance of Germ Theory

- 1860's and 1870's
  - Ubiquitious microscopic agents (germs) were responsible for specific diseases
    - Initially one out of many explanations and took some time to gain widespread acceptance
  - Koch's postulates
- Between 1880 and 1898
  - Identified microrganisms responsible for 20 diseases
    - Cholera, plague, and tuberculosis
- Early 20th Century
  - Breakthroughs on the importance of vectors
    - Malaria, yellow fever, plague

Early Developments in Modern Virology

- 1890's – Pioneers in virus research
  - Martinus Beijerinck, Dmitrii Ivanovsky, Adolf Mayer
    - Tobacco mosaic virus (TMV)
      - First demonstration of "filterable agents"
      - Too small to observe under light microscopy but able to cause disease by multiplying in living cells and tissues
- 1898 – Loeffler and Frosch
  - Description of the first filterable agent isolated from animals
    - Foot-and-mouth disease
- 1901 – Walter Reed
  - Recogniton of the first filterable agent in humans
    - Yellow fever
- 1901 – First influenza virus isolated
  - Chickens - fowl plague
  - Not recognized as an influenza virus until 1955
  - Now classified as an A/H7N7

Lustig A., Levine A.J.. One hundred years of virology. J Virology August 1992. 66(8): 4629-31.

Early Vaccine Development

- Pasteur demonstrates creation of standardized, reproducible vaccines on the laboratory
  - Chicken cholera (1880), anthrax (1881)
- Human vaccines
  - Rabies (1885)
  - Typhoid (1896)
  - Cholera (1896)
  - Plague (1897)
- Notable advances in immunology at the end of the 19th century
  - Theroy of cellular immunity (Elie Metchnikoff 1884)
  - Paul Ehrlich
- Heady time for medicine!

Russian Flu Pandemic 1889

- First influenza pandemic in the modern connected world
  - First with mapping*
    - Modern transportation (e.g., railroads and steamships)
    - Central Asia (Bokhara)
      - Herald wave – May 1889
        - Seed infection of a local population with novel influenza
      - First wave – fall and winter of 1889
        - Exploding out of Russia in October 1889
        - Spread throughout the Northern Hemisphere within 4 months
        - Deaths peaked in the US by the 2nd week in Januay
      - Followed by 2 more waves ending in 1892

*Patterson, K. David. *Pandemic Influenza 1799-1900: A Study in Historical Epidemiology*. Totowa NJ. Rowman and Littlefield. 1986

Russian Flu Pandemic 1989

- Uneven records*
  - Very high morbidity
  - European mortality estimate at least 250,000 deaths
  - Worldwide mortality estimated at approximately 1 million deaths
  - Classic U-shaped mortality curve
    - Greatest in the very young and the elderly
- Palliative care is all medicine could offer
  - "Quack" remedies abounded

*Patterson. *Pandemic Influenza 1700-1900*

Russian Flu Pandemic 1889
Etiology

- Contemporary medical researchers identified an organism found in several victims with severe pneumonia
  - Pfieffer's bacillus
    - Bacillus influenzae
    - *Haemophilus influenzae*
    - Unsuccessful attempt at creating a vaccine
- Mid-20th century researchers conjectured causative agent as Influenza A H2N2 however recently determined as Influenza A H3N8

Early 20th Century

- Seasonal occurrence with occasional epidemics (e.g., 1900)
- Influenza doesn't generate great research interest
  - Seen as an annoyance more than a threat
- **Until…**


CLOTHES

The Spanish Flu 1918-1919

- Estimated 1/3rd of world's population (~500 million people) with clinically apparent infection
- Case-fatality rates were >2.5%
  - Usual case-fatlity rates associated with influena <0.1%
  - Total global mortality estimates range from 40 to as high as 100 million deaths
    - Total mortality estimates from The Great War (1914-1918) 9-10 million deaths

Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. Emerging Infectious Diseases. January 2006; 12(1): 15-22.

The Spanish Flu 1918 - 1919

- India and Pakistan
  - Average population growth from 1901-10 and 1921-30: 8.35%/decade
  - Apply to 1911 population expect growth to be 25.3 million from 1911-20
  - Actual growth: 2.7 million people
    - Difference of 22.6 million people

Davis, Kingsley. *The Population of India and Pakistan*. Princeton University Press 1951; app. B: 217.

Influenza and Pneumonia Mortality*
US and NJ, 1918-1919

	Expected # of deaths Last 4 months of 1918	Actual # of deaths Last 4 months of 1918	Expected # of deaths First 6 months of 1919	Actual # of deaths Last 6 months of 1919
United States**	27,763	309,920	62,266	119,939
New Jersey	1,570	18,842	3,187	5,839

*Bureau of Census. Mortality Statistics, 1919. Washington DC; Government Printing Office. 1921: 30-31. Expected deaths based on corresponding data from 1915
**Registration states as of 1915 excluding North Carolina (24 states) and including the District of Columia

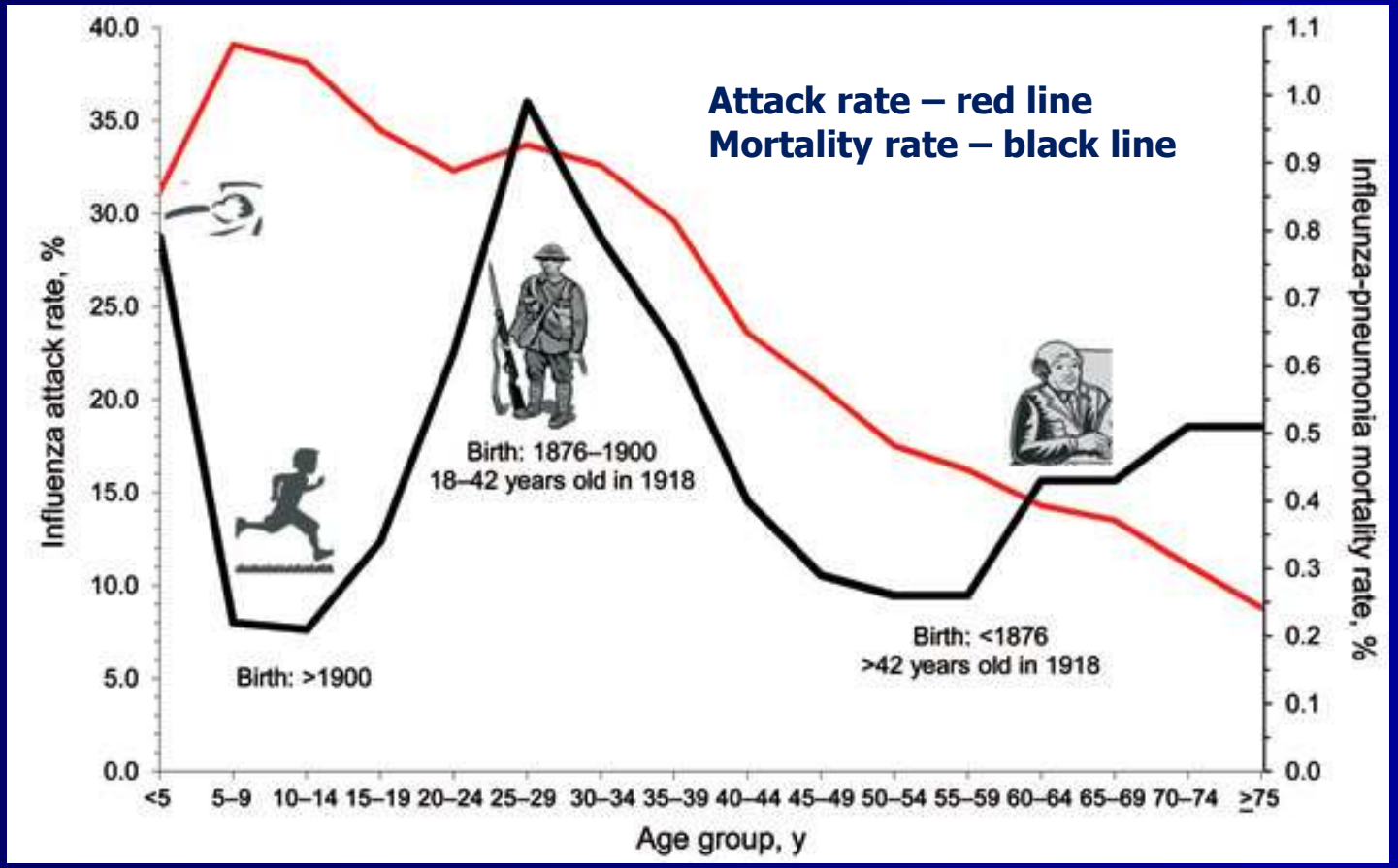
Influenza and Pneumonia Mortality*
US and NJ, 1918-1919

	Total excess deaths September 1918 to June 1919	Excess death rate per 100,000 Last 4 months of 1918	Excess death rate per 100,000 First 6 months of 1919	Excess death rate per 100,000 September 1918 to June 1919
United States**	339,839	439.8	88.6	528.4
New Jersey	19,924	564.4	84.9	649.3 4th highest rate

*Bureau of Census. Mortality Statistics, 1919. Washington DC; Government Printing Office. 1921: 30-31. Expected deaths based on corresponding data from 1915
**Registration states as of 1915 excluding North Carolina (24 states) and including the District of Columia

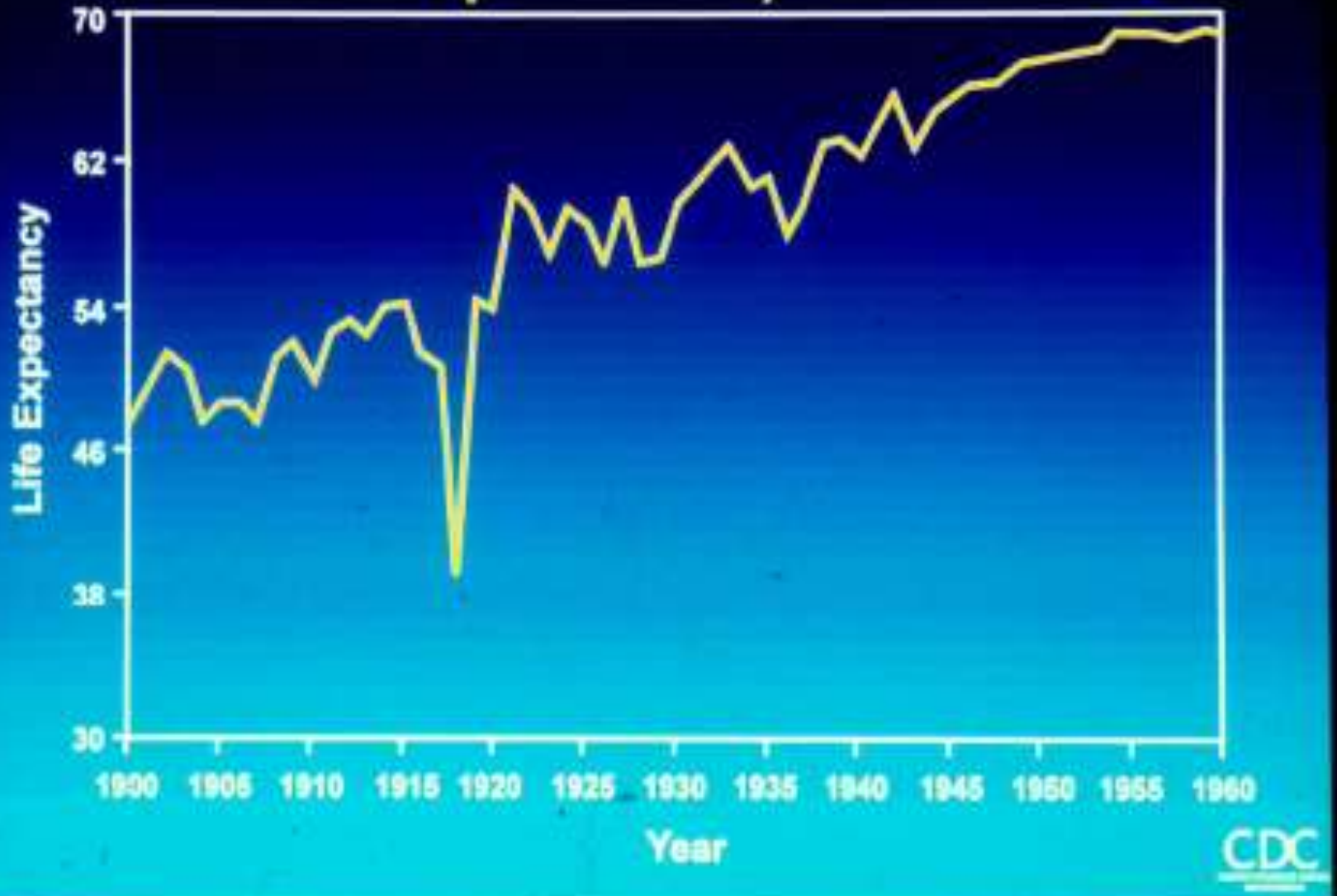
W-Shaped 1918 Influenza Mortality Curve

Unique Features



Shanks G. et al. Emerging Infectious Diseases 2012; 18(2):201-207

U.S. Life Expectancy 1900-1960



Population Effects

- Tanzania
  - Pandemic arrived at the start of planting season
  - Estimated mortality at 10% of total population
  - Failure to plant crops
  - Famine for the following 2 years

Ellison, James G. A fierce hunger: tracing the impacts of the 1918-19 influenza in southeast Tanzania. in *The Spanish InfluenzaPandemic of 1918-19: New Perspectives*. Edited by Howard Phillips and David Killingray. London: Routledge, 2003: 221-29.

The Spanish Flu 1918 - 1919

- Extremely virulent
  - Rapid progression from onset of infection to severe viral pneumonia
    - Fluid-filled, hemorrhagic lungs on autopsy
    - Most commonly associated with the second wave but seen in all three waves
  - Secondary bacterial pneumonia was common

The Spanish Flu 1918 - 1919

- A genotypic basis explaining it's severe virulence has not been identified
  - Neither the 1918 hemagglutinin (HA) or neuraminidase (NA) genes demonstrate mutations associated with increased tissue tropicity that account for increased virulence of other influenza viruses
    - highly pathogenic avian influenza H5 or H7 viruses
  - Possible cytokine dysregulation
    - NS1 protein associated with type 1 interferon inhibition
    - NS1 protein may be associated with an enhanced proinflammatory response (TNFalpha)

Taubenberger JK. The origin and virulence of the 1918 "Spanish" influenza virus. Proc Am Philos Soc. March 2006; 150(1): 86-112.

The Spanish Flu 1918-1919

- Pandemic spread essentially simultaneously wotld-wide in 3 distinct waves within a 12 month period
  - Distinct waves of transmission during influenza pandemics usually occur over 2-3 years
- First wave – Spring 1918
  - Best described in the US in March 1918
  - Less fatal than the 2nd and 3rd waves – "the 3-day fever"
- Second wave – September to November 1918
  - Highly fatal – "the purple death"
  - Simultaneous outbreaks in the Northern and Southern hemispheres
    - Encircling the entire world
- Thrid wave – early winter of 1919

The Spanish Flu 1918-1919
Explosive Transmission

- Camp Devens
  - Military post about 30 miles west of Boston
    - Admissions to camp infirmary (September 1918)*
      - 2nd – 31
      - 7th – 95
        - Date of first admissions with Spanish flu
      - 10th – 142
      - 13th – 350
      - 15th – 705
      - 16th – 1,189
      - 17th – 1,056
      - 18th – 1,176
  - By the end of October
    - 1/3rd of the post contracted influenza and 787 died

Jordan, Edwin O. *Epidemic Influenza: A Survey*. Chicago: American Medical Association. 1927. Table 12; 101

"These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hosp. they very rapidly develop the most vicious type of Pneumonia that has ever been seen… One could stand it to see one, two or twenty men die, but to see these poor devils dropping like flies… We have been averaging about 100 deaths a day… Pneumonia means in about all cases death."

Roy Grist, a hospital physician at Fort Devens

Barry, John M. *The Great Influenza: The Epic Story of the Deadliest Plague in History*. New York, Viking, 2004. 187-88.

Emergency Hospital, 1918 Influenza Pandemic, Camp Funston, Kansas

Courtesy of the National Museum of Health and Medicine, AFIOP, Washington, D.C., Image NCP 1603

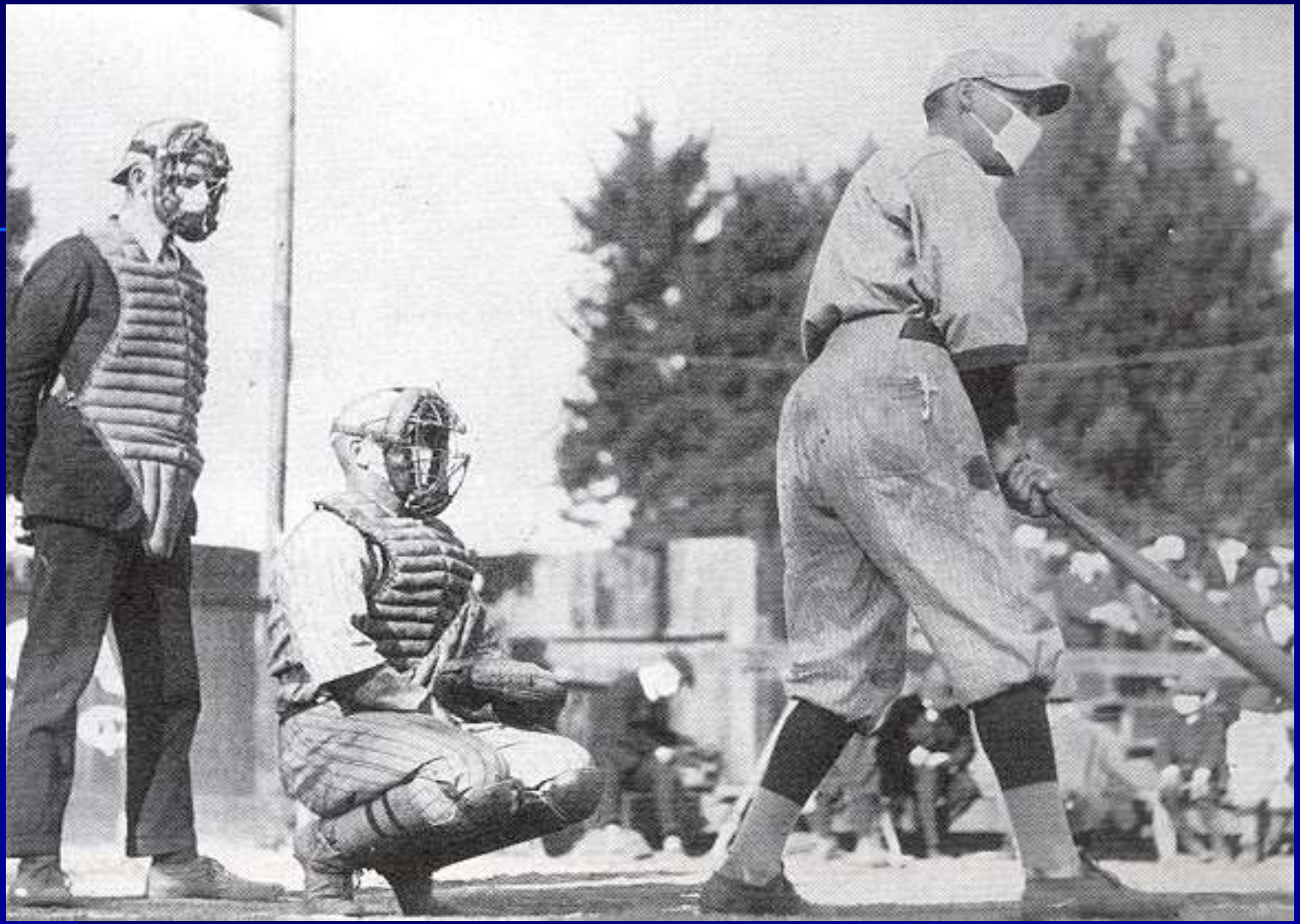
The Spanish Flu 1918-1919
Explosive Global Transmission

- Peak mortality
  - Boston and Bombay – October 1, 1918
  - Philadelphia, Liverpool, Prague, and Madras – October 19, 1918
  - San Fransisco, Dublin, Amsterdam, Rangoon – November 2, 1918

Jordan, Edwin O. *Epidemic Influenza: A Survey*. Chicago: American Medical Association. 1927; 103

The Spanish Flu 1918-1919
Search for Answers

- The medical research community was unable to explain or mitigate the pandemic
  - Early on determined Pfieffer's bacillus was not the responsible agent
  - Studies involving filterable agents inconclusive at the time
    - Likely problem was inconsistent technique
- Veterinarians suspected that a concurrent epidemic among swine in the US were caused by the same agent
  - Similar symptoms and appeared to follow the epidemic in humans




How to avoid Influenza
Gargle Daily

Search for Answers
Identification of the Virus

- 1931 – Richard Shope (Princeton)
  - Demonstrated that a filterable agent (e.g., the influenza virus) was responsible for the disease in swine[1,2]
- 1933 – Christopher Andrewes, Wilson Smith, Patrick Laidlaw (London)
  - Successfully transmitted influenza virus from humans to ferrets**
    - Thomas Francis Jr. confirms finding in 1934
- Within 5 years both groups demonstrate the swine influenza virus was the agent responsible for the 1918-19 pqndemic

[1]Shope, R.E., Swine influenza I: Experimental transmission and pathology. J Exp Med. 1931; 54: 349-59
[2]Shope, R.E., Swine influenza III: Filtration Experiments and etiology, J Exp Med 1931; 54: 669-84
[3] Smith W, Andrewes C, Laidlaw P.P., A virus obtained from influenza patients, Lancet 1933; 2:66-8

Identification of the 1918 Influenza Virus

- Influenza A (H1N1)
- Most likely nearly simultaneous transfer from of as yet unknown avian source to humans and swine in or around 1918
  - Early divergence between human and swine viruses
- All human influenza disease since 1918, including drifted variants and reassorted H2N2 and H3N2 viruses are descendants of the 1918 pandemic strain

Taubenberger, Jeffrey K., 1918 influenza: the mother of all pandemics. Emering Infectious Diseases, January 2006;12(1): 15-22
Zimmer, S.M., Burke, D.S., Historical perspective – emergence of influenza A (H1N1) viruses. N Engl J Med, July 16 2009; 361: 279-85

Search for Answers
Vaccine Development

- 1932 – Edward William Goodpasture
  - Introduced the use of the chorioallantoic membrane of a fertile hen's egg as effective medium for viral replication and growth
    - more efficient, safer, and cheaper than previous methods

Search for Answers
Influenza A Vaccine Development

- 1936
  - Frank Horsfall. Alice Chenoweth
    - Developed a live virus vaccine in mouse lung tissue
      - Demonstrated transient protection in humans
      - Considered unsafe as developed in mouse tissue
  - Development of 2 vaccines in embryonated eggs
    - Wilson Smith – live vaccine
      - 1937 - administered in humans (Soviet Union)
        - 20% of recepients developed febrile influenza
    - Thomas Francis and Thomas Magill – killed, whole virus vaccine

Eve of War

- Great concern in the military over influenza
  - January 1941: the Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army
    - Eventually renamed the Armed Forces Epidemiological Board (AFEB)
    - Thomas Francis Jr,. Jonas Salk, Albert Sabin, John Rodman Paul
    - Developed an influenza vaccination program

Influenza A Vaccination in the United States

- Process
  - Growing virus in fertilized chicken eggs
  - Inactivation of virus
    - Formaldehyde or formalin
  - Concentration of material and injection
- 1943: large scale study in soldiers
  - Vaccine protection rate was 70%
- By 1945 all military personnel were being vaccinated
- Vaccine was licensed for use in the US

Vaccine Failure - 1947

- Vaccine did not provide protection during the 1947 epidemic
  - Determined the strain first appeared in Australia at the end of 1946 and by March 1947 was widespread in the US
- Two impotant lessons
  - Influenza strains change
  - Initially arises in one geographic area and then can spread widely and rapidly

Vaccine Failure - 1947

- Antigenic shift
  - Subsequently found to be due to a drifted variant of the circulating strain
    - Initially named "A Prime" strain
    - Influenza A/Fort Monmouth/1/1947 (H1N1)

Influenza A Vaccine Development
Live Virus Vaccine

- 1940s – Frank Burnet and D.R. Bull
  - Live, attenuated virus could be produced in embryonated eggs
    - Mutated rapidly
    - Vaccines were not reliably attenuated and often produced disease
- 1960s
  - Live, attenuated vaccine produced found safe in adults
    - Could not be used in children
- 2003
  - Cold-adapted attenuated influenza vaccine developed by Hunein Maassab approved for use in the US

Influenza A Vaccine Development

- End of 1968 – Edwin Kilbourne
  - Introduced a new vaccine production technique
    - Reassortant technology
    - Concerns over risks of inadvertently producing novel human-transmissible, lethal strains

Kilbourne, Edwin. Future influenza vaccines and the use of genetic recombinants. Bulletin of the World Health Organization 1969; 41: 643-5

Influenza A Vaccine Development
Inacivated Vaccines

- 1970's
  - Subviron or split virus preparations
    - Solvent (ether or a detergent) used to dissolve viral lipid envelop
    - Less reactogenic than whole cell preparations
- Monovalent, bivalent, trivalent, quadrivalent, and pentavalent preparations
  - Since 1978
    - Trivalent vaccines: A(H1N1), A(H3N2), B virus

Pandemic Influenza Prevention/Mitigation

- Global surveillance
  - established in 1948
  - 142 national influenza centers in 113 countries
    - year-round surveillance
    - study influenza disease trends
    - send influenza viruses to the 5 World Health Organization (WHO) Collaborating Centers for Reference and Research on Influenza
      - Atlanta, Georgia, USA (CDC)
      - London, UK (National Institute for Medical Research)
      - Melbourne, Australia (Victoria Infectious Diseases Reference Laboratory)
      - Tokyo, Japan (National Institutes for Infectious Diseases)
      - Beijing, China (National Institute for Viral Disease Control and Prevention)

Pandemic Influenza Prevention/Mitigation

- Vaccine development and production capacity
  - Vaccine viruses must be tested and available in time to allow for full-scale production
    - 6 months to produce sufficient amount of vaccine
    - Dependent on fertilized egg production
  - Distribution to the public
    - Market vs centralized government control
    - High risk people vs everyone
      - February 2010 - ACIP recommends universal immunization for all persons $\geq$ 6 months of age
    - Annual immunization efforts?
      - Maintaining production capacity

Asian Flu Pandemic of 1957
"Don't Kill the Roosters"

- First pandemic in the era of modern virology
  - Initial recognition
    - NY Times article in April 1957 describing an outbreak in Hong Kong affecting 250,000 people over several days
  - Avian - Human reassortant virus
    - Novel HA and NA of avian origin
    - H2N2
  - Global estimated excess mortality attributable to 1957-59 pandemic[1]
    - 1.1 million deaths (95% CI, 0.7 million to 1.5 million)
    - Latin America experienced the highest rates, Europe the lowest
    - Greatest increases from baseline mortality rates seen in schoolage children and young adults but elderly not spared
    - Women in the 3rd trimester of pregnancy were found among the most vulnerable
- Replaces the H1N1 circulating strain until….

[1]Viboud C,. Simonsen L., et influenza pandemic al., Global mortality impact of the 1957-1959 influenza pandemic. J Infect Dis. March 2006; 213(5): 738-45

Hong Kong Influenza Pandemic of 1968
The "Smoldering" Pandemic

- Similar to 1957, initial recognition was via the media
  - Times of London reported on an outbreak in Hong Kong in July 1968
    - Global spread over 2 waves from 1968-70
      - Second wave more deadly than the first
    - Sporadic and variable impact in different regions
      - High morbidity and mortality seen in the US
  - HA is novel (avian origin) with NA derived from circulating H2N2 strain
    - H3N2
    - Speculation as to the retained N2 may have mitigated the impact of the virus
- H3N2 strain replaced the 11-year reign of H2N2 and remains a circulating "seasonal" strain

Pandemic Prevention Efforts in 1957 and 1968 Fall Short

- Global surveillance apparatus failed to detect the novel strains until they became regional epidemics
  - Vaccine production of novel virus vaccine in sufficient quantities takes several months
    - Lagged behind the pandemics
- The pandemic peaked before the majority of vaccine was released
  - Manufacturers were left with large amounts of unsold vaccine
- Problems with equitable distribution of available vaccine in the US
- Skeptical public

"Flu to the Starboard! Man the Harpoons! Fill with Vaccine! Get the Captain! Hurry!"

Edwin Kilbourne
New York Times, February 13, 1976
Pg 32, Column 4

1976 Swine Flu Vaccination Program, United States

- January 1976
  - Outbreak of respiratory disease in military recruits at Fort Dix, NJ
- February 1976
  - Isolates sent to CDC for identification
    - Influenza A/Victoria/75 (H3N2)
      - Known circulating strain
    - February 10 – Influenza A/New Jersey/76 (H1swN1)
      - Similar to the 1918 pandemic strain
      - 1 death, 13 hospitalizations, and serologic evidence of person-to-person transmission to 230 people at Fort Dix
      - No subsequent evidence of any transmission of A/New Jersey/76 (H1swN1) outside the confines of Fort Dix

1976 Swine Flu Vaccination Program, United States

- CDC and ACIP recommend swine flu immunization for the entire population
- President Ford convenes expert panel (including Jonas Salk and Albert Sabin) and accepts the recommendation
- April 5, 1976 - National Influenza Immunization Program (NIIP)
  - Bivalent vaccine for the high-risk population
  - Monovalent vaccine for the general population

1976 Swine Flu Vaccination Program, United States

- Liability
  - Manufacturers could not get liability insurance, asked for government indemnification
    - 2 month delay in production
  - End of July – Legionnaires disease outbreak in Philadelphia
  - August 12 – Tort Claims Act was signed
  - Vaccinations began on October 1
- Guillain-Barré syndrome (GBS)
  - Moratorium on influenza vaccines announced on December 16, 1976
  - Vaccination of high risk individuals vs A/Victoria/75 (H3N2) resumes on February 7, 1977
- Immunized 45 million people in 10 weeks
- Swine flu pandemic failed to appear
  - Program labeled a "debacle" by the media

1976 Swine Flu

- World Health Organization
  - Recommends stratigies to numerous countries with vastly different capacities and resources
  - "wait and see" strategy

1977 Russian Influenza Pandemic - "The Red Flu"

- First noted in the Soviet Union in November 1977
  - First occurred in northeastern China in May 1977
  - Influenza A H1N1
- Mild illness characterized by typical influenza symptoms
  - Restricted to persons <25 years of age
  - Absence of circulating H1N1 viruses in humans since 1957
- Molecular characterization of the HA and NA antigrns revealed a remarkable similarity to those circulating in the early 1950s
  - Deep freeze?
  - Implied inadvertent escape from a laboratory
- Two circulating strains (H1N1 and H3N2) in humans simultaneously

The combination of the mass swine flu vaccination campaign with its perceived adverse consequences for a pandemic that never occurred in 1976 and a pandemic that did occur the following season that was likely due to human error created great public skepticism and dampened enthrusiasm for any centrally managed public health influenza mitigation efforts until the end of the 20th century

Avian Influenza

- End of the 20th century
- Sporadic human infection has occurred
  - Illness in humans ranges from mild to severe
  - Associated with contact with infected birds
    - Saliva, mucous and feces
  - Person-to-person transmission is rare
    - Limited, inefficient and not sustained
- Three types of avian influenza known to infect humans
  - H5, H7 and H9

Revival of Interest in Pandemic Influenza Prevention

- Concerns over pandemic due to highly pathogenic avian strains
- Development of WHO Pandemic Influenza Preparedness Plans
  - Frequent revisions
  - Phasic approach
  - Serves as template for national strategic plans
- Global surveillance
  - Enhanced animal surveillance
    - Detection and interruption of transmission in domestic fowl and swine
      - Culling of the flock
        - Severe economic effects
  - Local orientated
    - Enhance local laboratory capacities
    - Send experts to the locality to assist in mitigating spread
      - Barricade vaccines (heterosubtypic protection) and antivirals
- Advances in vaccine technology and strategy
  - Preparation of high-yield seed reassortant viruses of all subtypes (H1 – H16)
  - Reverse genetic technology
  - Universal vaccine

Antiviral Medications

- M2 inhibitors
  - Influenza A only
    - Amantadine – 1974
    - Ramantadine – 1994
- Neuraminadase inhibitors
  - Influenza A and B
    - Oseltamivir – 1999
    - Zanamivir – 1999
    - Peramavir - 2014

2009 Swine Flu Pandemic

- In April 2009, near the end of 2008-09 seasonal influenza season the CDC reports of 2 epidemiologically unlinked human cases of a novel swine-origin influenza A (H1N1) virus (S-OIV)
  - Derived from a new reassortment of 6 gene segments from the known triple reassortant virus (contains human, swine, and avian gene segments) currently circulating in swine in North America and 2 gene segments (NA and matrix protein) from the Eurasian Influenza A (H1N1) swine virus lineage
    - A/California/04/2009 (H1N1)
- April 25 – WHO declares a public health emergency of international concern
- April 26 – US declares a public health emergency
- April 29 – WHO raises pandemic influenza alert from phase 4 to 5
  - Indicates the occurrence of human-to-human transmission in at least 2 countries in the WHO region
- June 11 – WHO raises pandemic influenza alert from phase 5 to 6
  - Indicates pandemic: increased and sustained transmission in the general population

Novel Swine-Origin Influenza A (H1N1) Investigation Team. Emergence of a novel swine origin influenza A (H1N1) virus in humans. M Engl J Med 2009;360:2605-15

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- Barry, John M., *The Great Influenza: The Epic Story of the Deadliest Plague in History.* New York. Viking, 2004
- Dehner, George, *Influenza: A Century of Science and Public Health Response.* Pittsburgh. Pittsburgh University Press, 2012
- Davis, Kenneth C., *More Deadly Than War: The Hidden History of the Spanish Flu and the First World War.* Henry Holt and Company, due for release on May 15, 2018
- Emerging Infectious Diseases. *Influenza.* 12(1), January 2006

“There’s nothing more predictable about flu than it’s unpredictability”

Arnold Monto
Epidemiologist
University of Michigan School of Public Health