The 1918 Flu Epidemic

“I had a little bird and his name was Enza
I opened up the window and in flew Enza”

Children’s rhyme, 1918
Some Grim Statistics

- **The 1918 influenza pandemic:**
  - Killed more than 20 million people worldwide. [Some estimates range as high as 75 million.] By conservative estimates this was almost 2.5% of the world population.
  - Killed 675,000 Americans (550,000 excess deaths).
  - Preferentially killed those between 21 and 29 years old.
  - Lowered life expectancy in America in 1918 by 12 years (48 to 36 years for men, 54 to 42 for women).
  - Accounted for 80% of American battle deaths in World War I.
  - Killed more Americans than died in World War I, World War II, the Korean War and Vietnam combined (423,000).
  - Killed more people in two months than the Black Death did in one year.
  - *Is almost completely forgotten.*
How does the 1918 pandemic stack up?

<table>
<thead>
<tr>
<th>Date</th>
<th>Historical Name</th>
<th>Death toll (estimate)</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>429–426 BC</td>
<td>Plague of Athens</td>
<td>75,000–100,000</td>
<td>typhus (?)</td>
</tr>
<tr>
<td>1665–1666</td>
<td>Great Plague of London</td>
<td>100,000</td>
<td>plague</td>
</tr>
<tr>
<td>1629–1631</td>
<td>Italian Plague</td>
<td>280,000</td>
<td>plague</td>
</tr>
<tr>
<td>1968–1969</td>
<td>Hong Kong flu</td>
<td>1,000,000</td>
<td>influenza</td>
</tr>
<tr>
<td>1957–1958</td>
<td>Asian Flu</td>
<td>2,000,000</td>
<td>influenza</td>
</tr>
<tr>
<td>165–180</td>
<td>Antonine Plague</td>
<td>5,000,000</td>
<td>smallpox(?)</td>
</tr>
<tr>
<td>541–542</td>
<td>Plague of Justinian</td>
<td>25–50 million</td>
<td>plague</td>
</tr>
<tr>
<td>1960–present</td>
<td>HIV/AIDS pandemic</td>
<td>&gt; 30,000,000</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>1918–1920</td>
<td>1918 Spanish Flu</td>
<td>75,000,000</td>
<td>Spanish Flu Virus</td>
</tr>
<tr>
<td>1331–1353</td>
<td>Black Death</td>
<td>75–200 million (30–60% of population)</td>
<td>plague</td>
</tr>
</tbody>
</table>
Unanswered Questions

• Where did it start?
• How did it spread so quickly and worldwide?
• Why was it so lethal and so contagious?
• Why did it preferentially kill those between 20 and 40 and not the very young or very old?
• Could it happen again?
An Introduction to the Spanish Flu
The Spanish Flu came in Three Waves
The First Wave

• Spring 1918: an epidemic of flu ("grippe") passed through the U.S.
• It first appeared in March in America.
  • ("patient zero" is generally accepted to be Albert Gitchell, a soldier stationed at Camp Funston, Kansas, who reported sick on March 4th. By lunchtime there were over a hundred cases; in a week the camp’s chief medical officer requested a hangar to house the patients.)
• It appeared quite ordinary, with mild symptoms.
• But it wasn’t. Autopsies on victims showed unusual hemorrhagic edema in the lungs, and it affected young adults more than others.
The First Wave Spreads:

- March 4\textsuperscript{th}: first appearance in Kansas
- Later in March: flu appears in Fort Dix, New Jersey; 15\textsuperscript{th} U.S. Cavalry en route to France reports 36 cases with 6 deaths.
- April 15\textsuperscript{th}: flu appears in Bordeaux, France (port of debarkation for AEF troops).
- May: flu appears in Bombay and Calcutta; also in China, New Zealand and the Philippines (half of Chunking down with flu; 3/4ths of dock workers in Manilla out with flu.)
- May 10\textsuperscript{th}: 90% of 168\textsuperscript{th} Infantry Regiment stationed at Dunkirk are affected as are 10% of the crew members of the Grand Fleet.
- June: flu appears in Portsmouth, England, with 31,000 cases in the British Expeditionary Force. Appears in Murmansk Russia following British troops arriving there.
- June 20\textsuperscript{th}: British assault on La Beque postponed because of flu.
- July: Thousands in Germany have flu; 214 deaths in Hamburg.
- By early summer, 10,000 ill in San Juan; by July it raced through troops in the Canal Zone; it arrived in Hawaii around the same time.
By late August 1918 the First Wave is worldwide. Armies in Europe call it “The Three-Day Flu”.

In America, though, the epidemic has waned. America, it seems, had dodged a bullet.

The *British Medical Journal* for July 1918 reports that “Influenza is no longer a threat.”

*But then something happened....*
...But first, some background on the flu virus.
An influenza A virus particle consists of:

- 7 separate strands of RNA, each assembled on a nucleoprotein matrix (ribonucleoprotein, RNP);
- A Nucleocapsid: protein capsule (M1, or Matrix protein) which encloses the RNA strands;
- A phospholipid membrane which was acquired from the host cell
- Several membrane proteins:
  - Neuraminidase (NA)
  - Hemagglutinin (HA)
  - M2 ion channels (M2:HA ratio 1:10 to 1:100)

Standard viral nomenclature: virus type/species from which it was isolated (if non-human)/location of isolation/isolate number/HA and NA subtype. Ex: A/Panama/2007/1999(H3N2) is isolate number 2007 of a human influenza virus taken in Panama in 1999.
Simple but Deadly: The Viral Genome

- The viral genome consists of 7 RNPs, numbered by increasing length:
  - Segments 1, 3, 4 and 5 each code for only one protein: two kinds of RNA polymerase, HA and the protein that binds the viral RNA (RNP).
  - Segment 2 codes for a third polymerase and, in some strains, an accessory protein that promotes apoptosis.
  - Segment 6 codes for NA.
  - Segment 7 codes for the M1 matrix and M2 ion transport channels.
The 1918 Flu Epidemic

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I opened up the window and in flew Enza”

Children’s rhyme, 1918
The influenza A virus: a perfect molecular machine

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Trojan Horse: Influenza enters the cell

- Hemagglutinin has a binding site for sialic acid.
- Sialic acid is found attached to the terminal sugar (e.g. galactose) of glycoproteins.
- The carbon 2 of the sialic acid can bind either to carbon 3 or carbon 6 of the galactose (α₂-3 or α₂-6).
- Influenza A hemagglutinin prefers the α₂-3 link, which is common in duck gut epithelium.
- While α₂-6 predominates in human respiratory epithelium, α₂-3 linkages are present, but mostly in the lower tract where airborne virus particles usually don’t reach.
Sialic Acid and its linkages

- α2-3 linkage
- α2-6 linkage

Neuraminidase attachment point
Life Cycle of Influenza A

1. NA binds to sialic acid, signaling the cell to absorb the virus.
2. The viral particle is engulfed in an endosome and subjected to an acidic environment. Here the low pH initiates a conformational change in HA causing the viral coat to fuse with the endosome membrane and open a pore; the M2 ion channel pumps H⁺ into the virus and releases the nucleocapsid with its genetic cargo.
3. Signals on the RNPs and proteins cause the cell to traffic them into the nucleus.
4. In the nucleus, viral polymerases use the vRNA(-) as templates to form
   1. mRNAs which then are used to form more viral proteins
   2. cRNA(+) which then uses the polymerases to form more vRNA(-)
5. Viral proteins accumulate on the cell membrane. M1 causes the membrane to bud off along with the nucleocapsid.
6. NA lyses sialic acid residues from the new particle so it won’t bind to other virus particles.
7. The rupture of hundreds of new virus particles causes the cell to die.
Mutations in Influenza A

• Viral RNA polymerases are notoriously inaccurate.

• If a cell is infected by more than one viral particles there can occur a mixing of the RNPs in the nucleus.

• This readily leads to rapid mutations in the very proteins that the immune system must recognize (NA and HA, and to a lesser extent M1), defeating any acquired immunity.

• It can also cause a mild form of influenza A to become more infectious and deadlier. The appears to be what happened in 1918.
First Wave vs Second Wave: Symptoms

- The first wave of the flu followed typical flu symptoms consisting of a three-day fever, a cough and a runny nose, followed by a rapid convalescence.

- The second and third waves were often fatal. Of every 1000 people who were infected, 800 had severe flu symptoms. The remaining 200 had lung complications, 120 of whom could be classified as desperately ill or dying.

- Normal flu symptoms accompanied by a very high fever, shivering and muscle aches quickly translated into lung complications, sometimes progressing to bronchopneumonia, which sometimes swept through the body like toxaemia or septicaemia. Dark spots would appear on the cheeks and patients would turn blue, suffocating from a lack of oxygen as lungs filled with a frothy, bloody substance. People literally drowned in their own fluids.
The Second Wave Begins

- Sometime in August 1918, after passing through a huge population, the virus mutated to a far more virulent and infectious form.
- Where it happened we likely will never know. But three nearly-simultaneous outbreaks of the new form give hints.
  - Were they three independent mutations?
  - Were they due to a single mutation that arrived in all three places at nearly the same time?
The Second Wave in Africa

- August 24th: H.M.S. Mantua arrived in Sierra Leone with 200 sick sailors (none died). By August 27th, 500 out of 600 Sierra Leone Coaling company workers stayed out with flu or caring for relatives with flu.

- In the week that followed, 75% of the British crew of the H.M.S. Africa, in port in Sierra Leone, contracted flu. Of those 580 or so, 51 died.

- H.M.S. Chepstow Castle, transporting New Zealand troops, reported 38 deaths after a stopover in Sierra Leone. The Tahiti, carrying naval ratings reported 68 deaths within two days of clearing Sierra Leone.

- Before September ended, 1072 people in Sierra Leone (about 3% of the population) had died of the flu.
The Second Wave in France

• Brest France, was the major disembarkation port for the AEF. In August of 1918 there were some 17,000 Americans in Brest, and the nearby AEF camp held 45,000 Americans.

• In the last days of August large numbers of French troops, many with the flu, arrived in Brest for training.

• The first cases of deadly flu appeared around August 22\textsuperscript{nd}. By September 15\textsuperscript{th} 1,350 sufferers were admitted to the hospital; 370 of them died.
The Second Wave in America

• The first reports came from Camp Devens, some 30 miles west of Boston, on September 8.

• The camp had been built for 36,000 troops, but now held 45,000 overcrowded men.

• On September 8th ninety flu patients came to the camp clinic. Then 500 a day; then 1,000 a day.

• By September 29th the clinic, built to handle 1200 patients, was treating 6,000, in bed after bed, row after row.
The Second Wave in America

• By mid-August over 14,000 soldiers at Camp Devens had sickened; 750 had died.

• Troop movements soon spread the disease to other camps in New Jersey (Fort Dix); Kansas (Camp Funston); New York (Camp Upton); and California and Georgia.

• Two servicemen arrived at Camp Dodge in Iowa on September 12th; six weeks later 12,000 men were infected; at one point the infirmary held 8,000 patients.
The Second Wave Spreads to Cities: Philadelphia

• In 1918 The Philadelphia naval base was the largest in the U.S., with a complement of 45,000 sailors.

• On September 7th, 300 sailors arrived from Boston.

• Two weeks later more than 900 sailors were sick.

• Then Philadelphia held a Liberty Loan campaign parade on September 28th.
  • 3,000 soldiers and sailors marched through streets crowded with over 100,000 close-packed cheering spectators.

• Two days later over 100 people a day were dying of the flu.
The Second Wave in America Spreads

• By October San Francisco reported over 1,000 deaths.
• Juneau Alaska declared a quarantine and ordered all arriving passengers to be examined dockside; but some arrivals were only in the early incubation period and passed the cursory inspection.
  • Soon it spread to remote native villages; half the population of the town of Wales (population 300) died; in Brevig, a native settlement of 80 people, 72 died of the flu.
  • By the end of 1918 Alaska reported over 3,000 deaths
The Second Wave in America: Grim Statistics

<table>
<thead>
<tr>
<th>City</th>
<th>Influenza Deaths</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Last 4 Months of 1918</td>
<td>First 6 Months of 1919</td>
<td>Total</td>
</tr>
<tr>
<td>Boston</td>
<td>4,949</td>
<td>1,549</td>
<td>6,498</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>2,299</td>
<td>908</td>
<td>3,207</td>
</tr>
<tr>
<td>New Orleans</td>
<td>2,363</td>
<td>1,089</td>
<td>3,452</td>
</tr>
<tr>
<td>New York</td>
<td>23,265</td>
<td>1,2437</td>
<td>35,702</td>
</tr>
<tr>
<td>St. Louis</td>
<td>2,883</td>
<td>1,199</td>
<td>6,965</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>13,426</td>
<td>3,237</td>
<td>16,663</td>
</tr>
</tbody>
</table>
Why was mortality so high?

Misdiagnosis, state of medical knowledge, overwhelmed facilities, etc.
Overwhelming numbers

- Try to imagine the consequences of 23,000 deaths in a four-month period in New York City with a population of about 5 million.
  - In all of 2006, 55,391 people died out of a population of 8 million.
- Morgues were full
- Gravediggers couldn’t keep up
- Coffins were scarce (laws were passed to prevent price-gouging)
- Hospitals were overwhelmed
- Vital services such as police and fire were crippled by shortages
PUBLIC NOTICE

In view of the severity of the present
Epidemic of Influenza

and in order that all efforts may be concentrated on the
stamping out of the disease, the local Board of Health,
after consultation with Kingston Medical Society and the
Mayor, has enacted that after Oct. 16th, and until further
notice,
1. Theaters and Moving Picture Houses shall be
   closed and remain closed
2. Churches and Chapels of all denominations shall
   be closed and remain closed on Sundays.
3. All Schools, Public or Private, including Sunday
   Schools, shall close and remain closed.
4. Hospitals shall be closed to visitors.
5. No public shall be admitted to courts except those
   essential to the prosecution of the cases called.
6. The Board advises the public most strongly not to
   crowd into street cars and to avoid as much as possible
   any crowded train or an assembly of any kind.

Provisions have been made by the Kingston Medi-
cal Society whereby all cases will receive the same either by
a final year medical student's visit. Therefore every case of ill
physician.
DEATHS AND NEW CASES ON INCREASE IN CAMPS; Disease Also Spreading Throughout Country—Federal Aid Rushed to Many States.

WASHINGTON, Oct. 18—With reports from all quarters indicating that the Spanish influenza epidemic is spreading, the Federal health authorities are intensifying their plans for cooperation with the health authorities of the various States in an effort to check the disease.

ORDERS ALL VACCINATED; Chicago Reports Increase in Deaths but Fewer New Cases.

Health Comr. Robertson orders general vaccination

NO SIGN OF ABATEMENT OF THE EPIDEMIC YET

DRASIC RULE IN CHICAGO; Will Arrest Persons Not Using Handkerchiefs in Sneezing.

Arrest ordered of persons not using handkerchiefs in sneezing

13,605 CASES IN CAMPS; Public Health Service Reports Show Disease Has Spread Over Country.

WASHINGTON, Oct. 6—Spanish influenza has spread to practically every part of the country. Reports to-day to the Public Health Service showed the disease is epidemic in many Western and Pacific Coast States as well as in almost all regions east of the Mississippi...

GRIP NOW SWEETING FORTY-THREE STATES; Drastic Steps Taken Throughout the Nation to Check the Epidemic. STOP PUBLIC MEETINGS Theatres Ordered to Close in Washington and All Gatherings Are Barred in Pennsylvania. Reports from Camps. 261 New Cases in Hoboken.

WASHINGTON, Oct. 3.—Reports received today by the Chief of the Division of Sanitation of the Surgeon General's office showed that the epidemic of Spanish influenza was unchecked in most of the army camps, and the Federal...
NEW GAINS IN GRIP HERE.; 999 Cases Reported Yesterday--Will Not Close the Schools.
For the twenty-four hours ending at 10 o'clock yesterday morning, 999 new cases of influenza have been reported to the Board of Health. From influenza there were forty-eight deaths, seventeen ...

Nov. 4, 1918

TO DEFEND CITY'S HEALTH.; Dr. Copeland Suggests Organization of Agencies and Citizens.
Weekly statistics gathered yesterday by the Department of Health show a marked decrease in the number of new cases of Spanish influenza and pneumonia. The health authorities predict a ...

Sept. 23, 1918

ARMY CAMPS REPORT 2,225 INFLUENZA CASES; Seven New Camps Send Records of Patients--Total Army Cases, 20,211.
Total report of cases in army camps

Oct. 17, 1918

MOVING MEN TO CAMPS DELAYED BY INFLUENZA
WASHINGTON, Oct. 17.—The Public Health Service is now actively directing the fight against Spanish influenza in thirty States, in addition to the whole of New England and the District of Columbia.

Oct. 7, 1918

INFLUENZA IMPEDES SHIP PRODUCTION; About 6,500 Workers Are Ill at Fall River and Hog Island--Other Yards Affected. NONE SOUTH OF BALTIMORE Schwab Sees Only a Temporary Check--Declares Shipping Outlook Is Bright. Schwab Greets Hurley, Lacks Shipped Workers. GAINS SLIGHTLY HERE. 903 New Cases of Grip Reported Yesterday--Use of Vaccine Not New
WASHINGTON, Oct. 7.—The epidemic of Spanish influenza has put 18 per cent. of the shipyard workers in the Fall River district and at least 8 per cent. of those at Hog Island, Philadelphia, temporarily on the ineffective list and is seriously interfering with rapid ship construction. Practically all of the yards as far south as Baltimore are affected to some degree, and extraordinary steps are being taken to fight the disease.

Sept. 28, 1918

BOSTON SITUATION BETTER.; 3,312 New Cases, However, in Outside Towns--Camps Improving.
BOSTON, Sept. 28.—Reports from forty-six cities and towns in this State outside of Boston showed 3,312 new cases of influenza and 103 deaths during the twenty-four hours ended at noon today. Conditions in army camps in New England were reported somewhat improved.

Sept. 27, 1918

NEW INFLUENZA CASES IN THE CITY DOUBLED; Number of Deaths in Twenty-Four Hours Equals Previous Total from July 1. HELP RUSHED TO BOSTON. Doctors and Nurses from Many Quarters to Combat Epidemic.
The number of new cases of influenza yesterday was double that of the preceding day and the Health Department is now concentrating on the effort to prevent the further spread of the disease. During the twenty-four hours...

Oct. 30, 1918

FAVORS RETAINING EMERGENCY HOURS; Copeland Points to Advantages Rule Has Worked in Reducing Traffic Congestion. 5,349 NEW INFLUENZA CASESCommissioner Attributes Sharp Increase to Duplications in Reporting Disease.
In a letter to the Public Service Commission, Dr. Royal S. Copeland, Health Commissioner, yesterday informed the body that he thought he would soon be able to discontinue his regulations concerning the opening and closing of business houses. Dr. Copeland pointed out the advantages which the plan had worked with respect to congestion of traffic and suggested that the emergency hours be made permanent if the traction companies would adjust their operation to them.
Misdiagnosis

• In the 1850s Louis Pasteur demonstrated that “microbes” caused fermentation, not spontaneous generation.
• By 1877 most scientists were convinced that bacteria caused disease (though not all physicians agreed even by 1918). Anthrax had been shown to be caused by a bacillus; soon after the bacteria causing throat infections, pneumonia and leprosy were identified. Vaccines were developed against many of the new bacteria.
• But some diseases could not be associated with a microbe; discharges from sick patients passed through fine filters to eliminate microbes still caused disease. The mysterious agents were called “virus” after the Middle English word for snake venom and the Latin word meaning “slimy liquid” or “poison”.
Misdiagnosis

• In 1892 two German microbiologists isolated a bacterium from influenza patients. They called it *Bacillus influenza*. (Today it is called *Haemophilus influenzae*).
  • It causes pneumonia, which indeed did kill most flu sufferers; but it does *not* cause flu.

• In 1918 *H. influenzae* was repeatedly isolated from Spanish Flu victims. It was widely thought to be the cause.
  • Vaccines against it were helpful but did not prevent Spanish Flu.

• Filtered discharge from flu victims usually caused flu in others, but there were several important experiments in which this was *not* the case.
The State of Medicine in 1918

Medicine was an art, not a science. Medical schools were many, but generally founded by groups of local doctors for profit, with no entrance requirements or often even exams; few if any were associated with academic institutions, much less hospitals, and so offered no clinical experience. Many doctors refuted the “germ theory” of disease; many still believed in bleeding. Thus physicians could offer little help in the flu pandemic. Most of the burden fell on nurses, who could only offer tenderness and comfort.
Unresolved Questions

• What made the flu so contagious and deadly?
• Why did it preferentially affect the 20 to 40-year-olds and not the very young or the old?
• Could it happen again?
• Why is it almost completely forgotten?
What made the flu so deadly?

- State of the art in medicine in 1918
- Misleading microbial diagnosis
- Complicating pneumonia
- Nature of the flu
  - Resurrection of the virus
    - Johan V. Hultin: Brevig, Alaska, 1951, 1997
    - Jeff Taubenberger 1997: PFC Roscoe Vaughan, Camp Jackson and Army Medical Museum.
  - Sequencing the virus: 2005
What made the 1918 H1N1 so deadly:
Reconstruction tests

Test viruses were constructed using genes from the 1918 virus and those from another influenza A virus (A/Tx/36/91(H1N1)) as follows:
- Tx/91 HA plus remaining 7 genes from 1918
- TX/91 with 1918 NA
- Tx/91 with both NA and HA from 1918
- Tx/91 with 1918 HA, NA, M, NP, and NS
- Two clones of the original 1918 virus

Note added in proof (by the authors): This research was done by staff taking antiviral prophylaxis and using stringent biosafety precautions to protect the researchers, the environment, and the public. The fundamental purpose of this work was to provide information critical to protect public health and to develop measures effective against future influenza pandemics.

The 1918 Flu Epidemic

“I had a little bird and his name was Enza
I opened up the window and in flew Enza”

Children’s rhyme, 1918
Spanish Flu in South River New Jersey
What made the flu so deadly?

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• Misleading microbial diagnosis
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What made the 1918 H1N1 so deadly: Hemagglutinin (HA) variant

- Hemagglutinin must first be cleaved by the host’s trypsin-like proteases for the virus to be infectious.
- Infectivity and pathogenicity of the virus is largely determined by the host’s trypsin-like proteases.
- The processing of hemagglutinin by these proteases takes place on the membranes of the host’s airway epithelial cells, where hemagglutinin is cleaved to produce HA1 and HA2 peptides.
  - The newly exposed N-terminal of the HA2 fusion peptide then acts to fuse the viral envelope to the cellular membrane of the host cell.
  - Most strains of influenza A are pneumotrophic, localizing the infection to airway epithelial cells, but a few strains can utilize trypsins on brain cells and multiply in both airway epithelial cells and in neuronal cells, causing life-threatening encephalitis, such as occurred in the devastating 1918 Spanish Influenza pandemic.
What made the 1918 H1N1 so deadly: Neuraminidase (NA) variant

• Neuraminidase promotes virus entry into host cells during the initial stage of infection and promotes the release of progeny virus from the host cell during the final stages of viral replication.

• When the reconstructed 1918 Spanish Influenza pandemic strain H1N1 was analyzed, the neuraminidase was found to directly bind plasminogen, sequestering the protease precursor to achieve a higher local concentration. The active form of the protease, plasmin, could then cleave and activate haemagglutinin, thereby promoting the viral infection of host cells.
Why did the virus preferentially affect 20 to 40 year-olds?

Cytokine Storm?

• Cytokines are small proteins secreted by a number of different cells in the body. They serve to signal other cells for various purposes. In the immune system, this signal can turn on or off various immune and inflammatory responses. They are the "first responders" in the lungs during a flu infection, where they can send out signals that attract more cytokines. Once the normal balance between immune and inflammatory responses is abrogated and inflammatory cytokines are produced in high concentrations a cytokine storm can result.

• This leads to the dilatation of small vessels and leak of body fluids through capillaries causing fluid accumulation in the soft tissues (edema) and in the lungs. This in turn leads to a decreased blood pressure. The release of these cytokines also causes fever. The entire picture resembles what occurs in sepsis. The result of all this is often fatal.

Dr. David Shlaes, Infectious disease expert and American Council advisor.

So: a robust immune system in this case is fatal.
Why did the virus preferentially affect 20 to 40 year-olds?

**Prior exposure??**

- The flu predominantly killed people between the ages of 20 to 40, i.e., those born between 1878 and 1898. During that period there were several pandemics, most notably the “Asiatic Flu” or “Russian Flu” of 1890-91. The first cases were observed in May 1889 in three separate and distant locations, Bukhara in Central Asia (Turkestan), Athabasca in northwestern Canada, and Greenland. The 1889-1890 Flu Pandemic claimed the lives of over a million individuals.

- Could this have primed the immune systems of exposed individuals leading to a cytokine storm?
  - Possibly but unlikely: recent studies seem to indicate that the Russian Flu was of the H3N8 subtype rather than H1N1 as was the 1918 Spanish Flu.
Lingering effects

• Woodrow Wilson initially supported a moderate peace with Germany

• In the middle of the Paris Peace Talks the third wave of flu struck Paris.

• It was around this time that Wilson abruptly changed from easy-going to irascible, forgetful and quick to judge. He ultimately agreed to the Draconian peace terms pushed by his European colleagues.

• Did the Flu change him? Did it trigger “transient ischemia attacks”?

• Did it lead to his massive stroke the following October which left him unable to persuade the U.S. government to ratify the Treaty of Versailles or to join the League of Nations?
“Using the 1918 pandemic as an exogenous shock we show that early disease exposure increases old-age mortality through noncancer causes and may trigger a trade-off in the risk for cancer and noncancer causes.”

Could it happen again?

• Origin of avian flu in China
• Deadliness of avian (H1N1) viruses
• Predicting next outbreak
  • Surveillance
  • Reporting problems
• Developing vaccines
  • Identifying the strain
  • Producing a vaccine
  • Distributing inoculations
  • Antigenic drift
Rice, Ducks, Pigs and People

• Much of rice grown in Asia is grown in open paddies.
• Ducks are used to keep down insects and snails.
• H1N1 influenza viruses are endemic in ducks, which, like most birds, use \( \alpha_2-3 \) sialic acid linkages in their intestinal tract cells. Humans have few \( \alpha_2-3 \) linkages and those are deeper in the respiratory tree, forming a natural barrier.
• After rice is harvested paddies are drained and often pigs are allowed in to clean up and wallow. Pigs have both \( \alpha_2-3 \) and \( \alpha_2-6 \) linkages.
• Thus pigs can acquire bird flu virus, which can mutate to use \( \alpha_2-6 \) linkage and thus become infective in humans.
Flu Pandemics in the 20th Century

• 1918 Spanish Flu (H1N1)
• 1947 (a “pseudopandemic”, primarily on military bases)
• 1957 Asian Flu (H2N2)
• 1968 Hong Kong Flu (H3N2)
• 1976 Swine Flu (H1N1) (Restricted to Fort Dix but led to panic vaccination of 43,000,000; later associated with Guillain-Barré syndrome)
• 1977 Russian (“Red”) Flu (H1N1). Predominantly affected <25 year-olds. Unexplained reappearance of H1N1, absent in humans since 1957. Inadvertent release of biological weapon?
• 1997 Bird Flu (H5N1): particularly dangerous as there was some direct bird-to-human transmission and high mortality.
A Short Recent History of Flu (Wikipedia)

• 1999: New Influenza A virus subtype H9N2 strain is detected in humans. It causes illness in two children in Hong Kong, with poultry being the probable source. No pandemic develops.

• 2002: New avian influenza A virus subtype H7N2 strain affects 197 farms in Virginia and results in the killing of over 4.7 million birds. One person is infected, fully recovered.

• 2003: Avian (Influenza A virus subtype H5N1) strain is reported in humans. Two people are infected in Hong Kong, one dies. By December 2006, over 240 million poultry would die or be culled due to H5N1.
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• 2003: First reported case of avian influenza A virus subtype H7N7 strain in humans. 88 people are infected, one dies. 30 million birds are slaughtered.

• 2004: New avian Influenza A virus subtype H7N3 strain is detected in humans. Two poultry workers become infected, eventually fully recovered.

• 2004: New avian influenza A virus subtype H10N7 strain is detected in humans. Two children become infected.

• 2004: Avian influenza A virus subtype H5N2 infects birds in Texas. 6,600 infected broiler chickens are slaughtered.

• (2005: George W. Bush unveils the National Strategy to Safeguard Against the Danger of Pandemic Influenza. $1 billion for the production and stockpile of oseltamivir [Tamiflu] are requested after Congress approves $1.8 billion for military use of the drug.)
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• 2005: Avian influenza A virus subtype H1N1 strain kills one person in Cambodia. In Romania, a village is quarantined after three dead ducks test positive for H1N1.

• 2009: New flu virus (H1N1) pandemic, first recognized in the state of Veracruz, Mexico, spreads quickly across the United States and the world, prompting a strong global public reaction. Overseas flights are discouraged from government health bodies. Worldwide, nearly 1 billion doses of H1N1 vaccine are ordered. A total of 74 countries are affected. 18,500 deaths.
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• (2012: American virologists Ron Fouchier and Yoshihiro Kawaoka intentionally develop a strain based on H5N1 for which no vaccine exists, causing outrage in both the media and scientific community.)

• 2013: Avian Influenza A virus subtype H7N9 strain breaks out in China. As of April 11, 2014, the outbreak's overall total would reach 419 people, including 7 in Hong Kong, with the unofficial death toll at 127.

• 2013: Avian Influenza A virus subtype H10N8 strain infects for the first time and kills one person.
## Timeline for Seasonal Vaccines

<table>
<thead>
<tr>
<th>Month</th>
<th>Task</th>
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<tbody>
<tr>
<td>January</td>
<td>Select strains</td>
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<tr>
<td>February</td>
<td>Produce virus</td>
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<tr>
<td>March</td>
<td>Purify and test</td>
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<tr>
<td>April</td>
<td>Fill and pack doses</td>
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<tr>
<td>May</td>
<td>Ship vaccine</td>
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<tr>
<td>June</td>
<td>Vaccinate patients</td>
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<td>July</td>
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<td>August</td>
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<td>November</td>
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<tr>
<td>December</td>
<td></td>
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<tr>
<td>January</td>
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</table>
Tracking the Flu

• Iowa Flu Prediction Market
• Google Flu Trends
• FluTrackers
Vaccine Problems

• Although vaccination is the primary strategy for the prevention of influenza, there are a number of likely scenarios for which vaccination is inadequate and effective antiviral agents would be of the utmost importance. During any influenza season, antigenic drift in the virus may occur after formulation of the year's vaccine has taken place, rendering the vaccine less protective, and outbreaks can more easily occur among high-risk populations. In the course of a pandemic, vaccine supplies would be inadequate. Vaccine production by current methods cannot be carried out with the speed required to halt the progress of a new strain of influenza virus; therefore, it is likely that vaccine would not be available for the first wave of spread of virus. Antiviral agents thus form an important part of a rational approach to epidemic influenza and are critical to planning for a pandemic.*

N Engl J Med 1997;337:874-880

*My emphasis
An initial 1997 study indicated that confirmed cases of influenza could be treated with zanamivir, demonstrating an approximately one-day reduction in the time to alleviation of symptoms. Subsequent studies in widely diverse geographic locations showed that when otherwise healthy adults with influenza received zanamivir or oseltamivir within 36 to 48 hours after the onset of illness, a decrease in symptomatic illness of one to two days occurred. One large study in the United States evaluated the efficacy of oseltamivir treatment in 629 healthy, nonimmunized adults 18 to 65 years of age who presented with a febrile respiratory illness of no more than 36 hours' duration, along with one respiratory and one constitutional symptom. Influenza was confirmed in 374 of the subjects, and oseltamivir treatment reduced the median duration of illness by more than 30 percent (from 4.3 days to 3 days) and the severity of illness by about 40 percent. There was a reduction in fever and a resolution of symptoms as soon as 24 hours after the initiation of treatment. Furthermore, treated patients had a lower frequency of secondary complications than did untreated patients.
“Tamiflu is heavily advertised, but many doctors believe that Tamiflu does not work well enough to justify the high cost of the drug, or the CDC recommendation that all patients take it. These doctors point out that there is very little high quality evidence that Tamiflu reduces the rate of serious complications from the flu.”

### Table 4. Percentage of Patients with Serious or Minor Adverse Effects Associated with the Administration of Neuraminidase Inhibitors.

<table>
<thead>
<tr>
<th>Drug and Use</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Zanamivir treatment*</td>
<td>Serious or life-threatening:</td>
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<tr>
<td></td>
<td>Allergic or allergic-like reaction, arrhythmia, bronchospasm,</td>
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<td></td>
<td>dyspnea, facial edema, rash, seizure, syncope, urticaria (&lt;1.5%)</td>
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<tr>
<td>Minor: Central nervous system: headache (2%), dizziness (2%)</td>
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<tr>
<td>Gastrointestinal system: nausea (3%), diarrhea (adults, 3%; children, 2%), vomiting (adults, 1%; children, 2%)</td>
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<tr>
<td>Respiratory system: sinusitis (3%), bronchitis (2%), cough (2%), other nasal signs and symptoms (2%), infection (ear, nose, and throat: adults, 2%; children, 5%)</td>
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<tr>
<td>Osimeltamivir treatment†</td>
<td>Serious or life-threatening:</td>
</tr>
<tr>
<td></td>
<td>Aggravation of diabetes, arrhythmia, confusion, hepatitis, pseudomembranous colitis, pyrexia, rash, seizure, swelling of face or tongue, toxic epidermal necrolysis, unstable angina (&lt;1%)</td>
</tr>
<tr>
<td>Minor: Central nervous system: insomnia (adults, 1%), vertigo (1%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system: nausea (10%), vomiting (9%)</td>
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<tr>
<td>Osimeltamivir prophylaxis‡</td>
<td>Similar to those reported during treatment, but generally with lower incidence</td>
</tr>
<tr>
<td></td>
<td>More common with prophylactic use: headache (20%), fatigue (8%), cough (6%), diarrhea (3%)</td>
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