INFLUENZA: HISTORICAL PERSPECTIVE AND MORE

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Executive Summary: Influenza pandemics have occurred regularly for at least the last 500 years. The influenza pandemic of 1918 was one of the most devastating outbreaks of disease the world had ever experienced. The current concerns generated by the avian flu outbreak in Asia have rekindled fears that the death and disruption caused by the great pandemic can happen again. Influenza is a constantly changing virus, which makes combating it difficult. Current knowledge about the virus, about how it infects and how it kills, is at a high level. The amazing re-creation of the 1918 pandemic virus revealed important clues as to why it was so deadly. As the scientific world races to combat the ever-evolving influenza virus, and as governments and businesses make contingency plans in case of a widespread outbreak, humankind apprehensively waits to see what this microscopic enemy will inflict upon us next.

Introduction

November 2, 2005
Flu Plan: Outbreak Could Restrict Travel
"Sustained person-to-person spread of the bird flu … anywhere in the world could prompt the United States to implement travel restrictions or other steps to block a brewing pandemic."
"President Bush outlined a $7.1 billion strategy to get ready for the next pandemic."

November 6, 2005
Anti-Bird Flu Cockfighting Bill Stalls

November 7, 2005
Beijing Poultry Markets Shut on Bird Flu Fears

November 10, 2005
U.S. Eyes Flu Vaccine-Booster Combo

November 16, 2005
China Confirms First Human Bird Flu Case

December 5, 2005
Bird Flu Fears Spread to Biotech Industry

December 12, 2005
Ninth Bird Flu Death in Indonesia

January 6, 2006
Third Sibling Dies of Bird Flu in Turkey

January 18, 2006
Nations Pledge $2 Billion to Combat Bird Flu
"Alarmed at the spread of bird flu beyond East Asia, nations pledged nearly $2 billion … to fight the disease."

February 8, 2006
Bird Flu Cases Reported in Nigeria
"A 'highly pathogenic' strain of the H5N1 bird flu virus has been found in poultry … in Nigeria—the first reported case of the disease in Africa …"

In the last six months, the news media has inundated us with almost daily headlines about the avian flu and its ever-widening spread. Headlines reflect the fear that it will cause the next flu pandemic and report on the preparations for its eventual arrival in the Western Hemisphere. Every winter, influenza is a fact of life. People are encouraged to get their flu shot. The Weather Channel tracks the states that have outbreaks on a color-coded map of the United States. Deaths due to influenza occur, mostly among the very old, the very young or the chronically ill. So what is different this year? What has led to an almost panic mentality among government and public health officials? To understand, one needs to look back almost 90 years to an event that until recently had not been a part of the collective memory of the country.

The 1918 Pandemic

First, some definitions:

- Epidemic—a seasonal outbreak of disease in a locality.
- Pandemic—a global outbreak of disease.

Recorded influenza epidemics have occurred since the 16th century. There have been 31 pandemics in the last 500 years. The 18th and 19th centuries each recorded at least three pandemics. The last pandemic of the 19th century (1889-1890) killed approximately 1 million people worldwide. But the world had never seen anything like the pandemic that occurred about the time the First World War was ending.

Exactly where the killer virus arose is not known. Various theories exist. Though many believe it originated in Asia, there is no evidence of an outbreak there at that time. Another theory places the virus in

the mid-Atlantic states as early as February 1918. Currently, the most credible theory postulates that the pandemic virus emerged in rural Kansas in March 1918. Though scientists cannot agree on its place of origin, one thing is clear—the 1918 influenza did not appear first in Asia, as have all the subsequent ones (i.e., 1957-58 Asian flu and the 1968-69 Hong Kong flu).

The 1918 influenza began with a warning wave. The first reported cases occurred at Camp Funston (now Fort Riley, Kansas) in March 1918. It spread worldwide by early summer, leading to tens of thousands of deaths. (Historical footnote—the name Spanish flu was also given to this pandemic because Spain, a noncombatant in the war, had a free [i.e., uncensored] press, which fully reported its ravages.) The soldiers sent from the United States to the European front carried the virus with them. So many soldiers became ill that it affected the conduct of the war. Men were too ill to fight and battle plans had to be altered. In June alone, Britain reported 31,000 cases among its troops. It is possible that the influenza may have hastened the end of the war since so many were ill. But the deaths that occurred in this first wave were nothing compared to what occurred later in the year.

In late August, sailors stationed in Boston began to exhibit symptoms of influenza. By September, 2,000 men of the First Naval District there had the disease. It then spread to the civilian population of Boston and, from there, across the United States. Within two months, it had circled the globe, leading to the following horrifying statistics:

- One-fifth to one-half of the world's population infected.
- 50 million to 100 million dead worldwide.
- Approximately 27 million people in the U.S. infected.
- 600,000 to 850,000 dead in the United States—a death toll exceeding the combined combat death toll from WW I, WW II, the Korean conflict and Vietnam war.
- 16 million dead in India.
- Entire Eskimo villages wiped out.
- 20 percent of Western Samoans died.

In 1918, the average life span in the U.S. fell by 12 years—from 51 years in 1917 to 39 years in 1918. The death rate for 15-34-year-olds was 20 times higher in 1918 than in previous years.

In a 16-week period, influenza killed more people than any disease outbreak in human history in a similar period of time. The mortality rate of most types of influenza is relatively low—about 0.1 percent. The 1918 flu had a mortality rate 25 times that—2.5 percent. The usual influenza has a U-shaped mortality curve, with the very old and very young most likely to die. The Spanish flu had a lopsided W-shaped curve with the expected number of deaths in the very young, a surprisingly a large number of deaths in those ages 20-40, and fewer than expected deaths in the frail elderly.

Luckily, most victims recovered after a more intense version of the aches, fever and chills of the usual flu. But those it killed, it killed swiftly. Those who died succumbed to a terrible pneumonia, in effect, drowning as a blood-tinged fluid filled their lungs. A doctor at a military base near Boston described the death process in a letter to a friend:

> *These men start with what appears to be an attack of … 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 …. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate.*

The intense cyanosis that was a hallmark of the Spanish flu is variably described in the literature as being lavender gray, dark brownish purple or a blue so deep that it was thought to indicate the return of the Black Death. The medical term is heliotrope cyanosis, named ironically for a beautiful, tiny, very fragrant, very blue flower. Fewer than 5 percent of those who developed heliotrope cyanosis survived. A nurse from that time reported that when patients arriving for treatment exhibited bluish toes and fingertips, she knew they would be dead before the next day.

The 1918 influenza affected pregnant women at a higher rate than it did other individuals. In some states, maternal mortality increased by over 50 percent. The percent of pregnancies ending in stillbirth increased from about 3 percent in September 1918 to almost 5 percent in October 1918. In an interesting study published in July 2005, a researcher presents the hypothesis that those individuals who were in utero at the height of the pandemic displayed "reduced educational attainment, increased rates of physical disability, lower income, lower socioeconomic status, as well as accelerated adult mortality compared with other birth cohorts." Based on this research, the pandemic had a lifelong effect on the children of the mothers who survived the infection.

Many major American cities were disproportionately affected. There was a breakdown in the social order as people, paralyzed by fear of the raging disease, did not help those who were ill. John Barry, in his book *The Great Influenza: The Epic Story of the Deadliest Plague in History*, reports that healthy

people were so panicked by the disease that they would not even check on their desperately ill neighbors.

Philadelphia was one of the hardest hit American cities. Nearly 13,000 people died there in a matter of weeks. Funeral homes were overwhelmed. Every morning, horse-drawn wagons moved though the streets with their drivers shouting, "Bring out your dead." The supply of caskets was inadequate and some victims were buried in mass graves. In Pittsburgh, one in every 100 died. When the epidemic was at its height, another person became ill every 70 seconds and a person died every 10 minutes. Even San Francisco, 3,000 miles away from the original outbreak, reported 23,639 cases with 2,122 deaths.

In October 1918, the Surgeon General of the Army warned, "If the epidemic continues its mathematical rate of acceleration, civilization could easily disappear from the face of the earth within a few weeks." Then just as quickly as it had appeared, it was gone. By the end of 1918, the epidemic was over. And what is even more amazing, it seemed to disappear from the collective memory of the country. In 1956, journalist H.L. Mencken offered this by way of explanation, "The epidemic is seldom mentioned, and most Americans have apparently forgotten it. This is not surprising. The human mind always tries to expunge the intolerable from memory, just as it tries to conceal it while current." Whether he was correct or whether there is some other explanation, the 1918 influenza pandemic faded from people's consciousness—until recently. Now with avian influenza in the news, awareness of the pandemic of 1918 is back and the big question is—can it happen again?

An Influenza Virus Primer

- The influenza virus is an endemic virus. It is present somewhere in the world at all times.
- While there are three separate types—A, B, C—type A is the one that causes the most severe outbreaks.
- Besides humans, influenza A can infect birds, pigs, cats, horses and seals. Influenza B and C infect only humans.
- Influenza is an RNA virus composed of eight separate segments. RNA viruses can reproduce only by commandeering the reproductive abilities of a host cell.
- Flu viruses have two distinct proteins projecting from their surface that allow the virus to attach to and enter a host cell.
    - o Hemagglutinin [HA]
    - o Neuraminidase [NA]
- When an individual is infected by influenza, his/her immune system reacts to produce antibodies to these proteins.
- The influenza virus A has developed mechanisms for changing these proteins so that a host's immune defenses can be evaded.
- At least 16 different H antigens and nine different N antigens have evolved. Most of these subtypes are found only in animals.
- The majority of human infections are caused by combinations of only the H1, H2, H3 and the N1 and N2 subtypes.
- Currently, type A influenza viruses are identified by type, host of origin (if other than human), place of origin, strain number, year of discovery and type of H and N antigen that they bear—for example, A/swine/Iowa/15/30 (H1N1).

During an infection, an individual's immune system produces antibodies to that flu virus's particular H and N antigen, thus conferring immunity to that influenza strain. Immunity to a flu virus close in genetic makeup to another subtype will confer some immunity to the second type. Unfortunately, influenza A is somewhat of a chameleon, easily changing the composition of its two antigens. As it changes, the antibodies that were previously effective against it become less effective.

Changes to the influenza virus can be either minor or major, called respectively:

- Antigenic drift
- Antigenic shift

Minor variations are referred to as drift and account for the need to develop a new influenza vaccine each year. The major changes—the shifts—can involve changes in the hemagglutinin alone or in both the hemagglutinin and neuraminidase. For example, in 1957 when influenza A changed from H1N1 to H2N2, it triggered a pandemic that resulted in 70,000 excess deaths in the United States. In 1968, only the hemagglutinin changed (H2N2 to H3N2), and the resulting outbreak was much less severe.

Scientists think that drift happens when mutations occur sequentially in the RNA segment that codes the hemagglutinin as the virus passes from one infected individual to another. On the other hand, the antigenic shifts that account for the emergence of the pandemic-causing strains cannot be explained on the basis of mutation alone. Given that the influenza genome has eight separate segments, the current thinking is that shift occurs when a human flu virus incorporates genes from an animal virus. This shift produces a virus with antigens that no human immune system has ever seen, leaving the human population open to widespread infection.

A current theory postulates that domestic pigs may provide the environment that fosters the antigenic shift and the creation of a new deadly virus. Though it

is difficult for avian flu viruses to infect humans, domestic pigs are easily infected by both human and avian viruses. If a pig is infected by both, it is possible for the viruses to exchange genetic material, producing a new virus.

The 1918 Influenza Virus

What was it about the 1918 virus that made it so deadly? There were no methods available to scientists of that time to answer that question. In fact, the influenza virus itself was not identified until 1933. It was not until recently that scientific methods and equipment existed that made an attempt to analyze the pandemic virus feasible. But to analyze a virus, one has to have access to the exact virus that caused the outbreak.

The impossibility of finding a living 1918 influenza virus was a fact. However, scientists were able to locate three sources that yielded fragments of the virus. Two samples of tissue taken from the lungs of two soldiers who died on September 26, 1918, were found in the archives of the Armed Forces Institute of Pathology. The final sample came from Brevig Mission, Alaska, a settlement that had lost about 85 percent of its population in one week in 1918. Dr. Johan Hultin, a pathologist, received permission to exhume the bodies of influenza victims that had been buried in the permafrost. The frozen body of an Inuit woman who perished yielded samples that contained fragmented RNA from the virus.

From the fragments, the genome was sequenced, and in 2005, researchers recreated the complete Spanish flu virus! This has not been without controversy since a deadly microbe that had mutated out of existence exists once more. However, scientists have been able to make the following determinations about the deadly virus:

- It was an entirely avian virus of the H1 subtype that developed the ability to infect humans. (In contrast, the viruses that caused the 1957-58 and 1967-68 pandemics contained both human and avian flu genetic material.)
- Changes in only 10 amino acids in the surface proteins of the 1918 avian virus allowed it to easily bind to and infect human cells, setting the pandemic in motion.
- It was extremely virulent. In mice infected with the recreated virus, after only four days, 39,000 times more virus particles were produced than a modern flu strain would trigger.
- It had the ability to permeate the entire lung, triggering an intense immune reaction marked by the release of a flood of chemokines and cytokines (i.e., proteins that trigger inflammation in response to infection) that caused the severe primary viral pneumonia that killed so many.

The Current Situation

The avian flu currently circulating in Asia (H5N1) is deadly. Though it exists naturally in the intestines of wild birds and usually does not make them sick, it has been discovered in its highly pathogenic form in dead migratory birds. It has been found in migrating birds as far away as Eastern Europe. In addition, it is extremely infectious and deadly to domestic birds. Through the end of 2005, humans have escaped widespread infection (it had been detected in fewer than 200 people). Unfortunately, it had killed approximately 50 percent of them.

The H5N1 virus is already beginning to exhibit some of the changes in amino acids in surface proteins that the 1918 virus did. Recent experiments have shown that it triggers the same tremendous increase in inflammatory proteins as the 1918 virus—though it is not the same virus. (The 1918 virus was an H1 virus; the current avian flu is an H5 virus.) Of course, if it mutates to allow human-to-human transmission, the process of mutating may also lessen its pathogenicity—but it may not.

A vaccine against it cannot be produced by using the current method of growing flu viruses in the embryos of fertilized eggs. It is a bird disease and it would kill many of the embryos. Can another method be found to quickly produce massive amounts of vaccine needed to protect the population? Interest is increasing in developing vaccine-making capabilities using cell cultures, but that would require a huge monetary investment to accomplish. Experts think that current antiviral medications would be effective against an avian flu infection. But if a pandemic occurs, will there be enough of it for everyone who needs it?

A test to quickly determine the type of influenza infecting an individual has been developed recently by a doctoral student at the University of Colorado. It gives a reliable answer in 11 hours as opposed to the four days it takes with the current technology and should be in laboratories worldwide by next year. It should prove invaluable at identifying those with the avian influenza so that decisions can be made quickly about who should be quarantined, who should get antivirals, and who should be vaccinated.

Possible Impact on Society

The concern about the next influenza pandemic has prompted the U.S. President to ask for $7.1 billion for programs to:

- Detect flu outbreaks before they spread.
- Purchase and stockpile vaccines.
- Develop new vaccine technologies.
- Prepare government agencies to respond to major outbreaks.

In 1999, the Centers for Disease Control commissioned a study to estimate effects of a new pandemic in the U.S. alone. The results were:

- 89,000 to 207,000 deaths.
- Up to 700,000 hospitalizations.
- Up to 42 million outpatient visits to health care professionals.

The economic impact on society would be on the order of $70 to $170 billion. An influenza pandemic could halt the normal, necessary activities of entire cities or nations. Even now, companies are being advised to update their business continuity plans, since employee illnesses could severely hamper operations. An article in an early November issue of *The National Underwriter* referred to grim stories in 1918 editions of their publication that reported life insurance companies processing death claims as their own employees were dying.

Estimates of losses that would be incurred by the insurance industry, if a pandemic on the order of the 1918 one occurs, range from $15 billion to $100 billion. In group life alone, it is estimated that claims would double from the $15-$20 billion now paid in an average year. Though the majority of those infected by a new pandemic influenza would probably survive (based on experience in past pandemics), the cost of caring for the ill would be quite high. Since it is estimated that up to 0.3 percent of the population would require hospitalization, it is possible that near 100 percent of the hospital beds for acute care would be taken by influenza patients. This would occur at a time when doctors, nurses and other health care workers would also be ill from the pandemic.

While there is no way of knowing if a new pandemic strain would cause the death and disruption seen in the 1918 pandemic, the world community is in a better position to deal with it than it was at that time. The culprit has been identified and is being monitored. Vaccines against it are being developed. Medications effective against influenza already exist. Plans are being made on the local, state and national levels to deal with a worst-case scenario. The next two years will present the most danger while the vaccine for the avian flu H5N1 is being developed.

But if the avian flu pandemic doesn't occur, or it does but isn't as severe as feared, we should not consider the danger eliminated. Influenza pandemics occur with regularity and, while they may not approach the severity of the great influenza of 1918, the world must be prepared. The current threat of influenza has once again revealed how vulnerable the human race is to ever-evolving infections. We have enjoyed a relative respite from the ravages that infectious diseases are capable of inflicting for the last 60 years. If our scientists cannot continue to develop methods of effectively combating them, the ever-evolving microbes will be the victors. Diseases—and not just influenza—that came to be considered minor problems in the last half of the 20th century will once again devastate the peoples of the earth.