The centenary of the “Spanish Flu”—Lessons for today

Part two

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The virulence of the disease

One of the most frequent questions that plagued scientists was why this pandemic was so deadly. The pandemics of 1847 and 1889 had epidemiologic similarities distinct from the 1918 pandemic. But at that time, scientists had not yet discovered viruses, and there were no laboratory tests to diagnose or detect them. Answers to this puzzle had to wait till the 1930s when the closely related influenza viruses known as H1N1 were first isolated from pigs and humans, and investigations as to the origin of the disease began to provide clues. It would be another 60 years before a breakthrough was achieved.

It has been presumed that the 1918 virus was highly transmissible and thus inherently lethal. Studies have shown that the infection rates during the 1918 pandemic were equal to infection rates during other pandemics in the last century.

Most of the pandemic-related deaths were not a byproduct of viral pneumonia or acute respiratory distress syndrome. Most infected individuals who succumbed died about a week or more after the onset of the illness. These deaths were due to secondary bacterial pneumonia caused by respiratory bacterial colonizers such as Streptococcus or Haemophilus influenza. The lethal secondary pneumonia are postulated to have been caused by an overreactive immune response caused by the influenza virus.

The authors Shank and Brundage hypothesized that what made the second wave of the 1918 pandemic so deadly for young adults was that they had a prior exposure to a similar strain, i.e., the 1889-1890 Russian pandemic. That viral strain may have shared with the 1918 virus a similar internal protein that antibodies attach to. Exposure to the 1918 virus then may have caused an overstimulation of their immune response. Those born after 1875 and before 1901 (the 18-33 age group) were most likely to succumb to secondary bacterial pneumonia during the pandemic of 1918.

Young children had the highest infection rates but not the same mortality rate because they had not been exposed to a similar virus and did not mount a severe immune response. The elderly may have developed antibodies to bacterial pathogens in their lifetime and had the ability to resist bacterial pneumonia. But susceptible young military recruits and citizens of the world brought into proximity by “the war to end all wars” succumbed to these factors at an unprecedented rate.

Shanks and Brundage, who developed this hypothesis that prior exposure led to an excessive inflammatory response, argued that this was essentially a unique event. In the modern era, the current populations interconnected by commerce and cultural activities have exposed people to such a wide range of viral and bacterial respiratory pathogens that their immune repertoire has diversified. Also, the capacity to create vaccines, arsenals of antibiotics and supportive care should prevent such deadly pandemics. These optimistic conclusions, however, don’t take into account the ramifications of political instability, war, and economic collapse.

The recent history of the flu virus

The H1N1 virus disappeared from human circulation after the Asian flu of 1957 (H2N2) where nearly 2 million people succumbed. The next major pandemic was the 1968-1969 Hong Kong flu which first broke out on July 13, 1968, killing an estimated one million people worldwide. It was caused by the H3N2 strain of the influenza virus. By September of 1968, the flu had reached India, the Philippines, Australia, and Europe. American soldiers returning from Vietnam brought the virus to the US, but it did not become widespread. Approximately 33,800 people died. The case fatality ratio remained low at 0.1 percent, making it a category two disease on the Pandemic Severity Index or PSI. (A case fatality ratio greater than 2.5 percent is considered a category five.)

H1N1 was to reemerge in 1977 and presently persists as two major lineages and as two additional reassortant lineages; human H1N1 lineage, porcine enzootic H1N1 lineage (classic swine flu) and the reasserted human H3N2 virus lineages. Reassortant viruses contain two or more pieces of nucleic acid from different parents. Such viruses are produced in cells co-infected with different strains of a given virus. The present descendants don’t have the same deadliness as the 1918 virus. All influenza A pandemics since the Spanish flu have been caused by descendants of the 1918 virus except the H5N1 bird flu virus. Recent pandemics in China have involved bird flu strains with H7N9 and H7N4. In 2004, the H5N1 bird flu began its assault spreading throughout Asia in just a few months then quickly moving into Europe, the Middle East, and Africa and the Americas by 2005-2006. The virus is contracted by exposure to infected birds though in rare cases human to human transition has been suspected. Case fatality rates were as high as 60 percent among those who contracted the virus. Today Egypt is considered the epicenter of human H5N1 infections. Animal model studies have shown similar pathogenic effects as the 1918 influenza virus which has the hallmark of an Avian-like virus. Scientist continues to speculate if the H5N1 virus could develop the capacity to spread between humans.

The 2009 H1N1 pandemic (the swine flu pandemic) was caused by a new version of the virus when a previous triple reassortment of the bird, swine, and human flu virus combined with a Eurasian swine flu virus. The infection was first recognized in the state of Veracruz, Mexico. Influenza spread globally, leading the World Health Organization and the CDC to declare the outbreak a pandemic.

It has been estimated that the global infection rate was 11 to 21 percent. The actual lab-confirmed deaths due to the pandemic are 14,286, setting the case fatality rate at 0.03 percent. But a model-based study in June 2012 indicated that the death related to the H1N1 influenza was fifteen times higher, with an approximate estimate of around 285,000 people killed, predominately in Africa and Southeast Asia, developing nations that lacked the advanced infrastructure to support the assault from a pandemic. Similar to the Spanish flu, 80 percent of the respiratory and cardiovascular deaths were in people younger than 65.

Genetic investigation of the 1918 flu

The characterization of the genomic sequence of the 1918 virus is credited to Ann Reid, a scientist with the Armed Forces Institute of Pathology at that time, and Jeffery Taubenberger, an American virologist. Work on acquiring fragments of the 1918 virus began in the mid-1990s when laboratory techniques in genomic sequencing had developed to the degree that such projects became feasible. The first positive signal came from an autopsy tissue belonging to an Army private named Roscoe Vaughn who died on September 26, 1918 at Camp Jackson, South Carolina, from pneumonia. They were able to locate the virus in his right lung.

By 1997 they had a full sequence of the hemagglutinin (HA) gene but did not have sufficient tissue to characterize all ten genes. In September of that year, they located virus in a second autopsy specimen from a private named James Downs who succumbed to influenza at Camp Upton, New York.

A retired pathologist by the name of Johan Hultin happened to read these preliminary reports on the investigation into sequencing the 1918 virus. He had tried to isolate the 1918 virus from victims buried in the Alaskan permafrost in 1951. He contacted Taubenberger and offered to return to Brevig, Alaska with a team. They were able to locate the remains of a thirty-year-old obese woman whose lungs had remained intact. With these specimens, they had sufficient material to sequence the complete 1918 virus.

In a paper published in 2011 in *PLoS Pathog*, Watanabe and Kawaoka explained that by using advancement in reverse genetics they were able to re-create the 1918 virus entirely from complementary DNAs that are synthesized from a single-stranded RNA as a template. With an artificially resurrected and intact virus bearing all eight RNA segments, molecular analysis into the unusual virulence of the 1918 pandemic was possible.

Initial testing in mice and non-human primates demonstrated a very high replication rate in the host that spread quickly throughout the respiratory tract. Like the autopsy reports on the patients in 1918, these laboratory animals had the hallmarks of acute respiratory distress that included lung edema and hemorrhage into the lungs. In the non-human primates, the virus triggered the expression of genes that led to a robust inflammatory response that caused the injuries they documented. Mice inoculated with the 1918 virus and the H5N1 avian influenza viruses have demonstrated uncontrolled immune responses, a hallmark of a highly pathogenic influenza viral infection.

The hemagglutinin (HA) is a viral surface glycoprotein that has two functions in the early stages of replication—receptor binding and membrane fusion. Though the 1918 virus HA sequence doesn't have a specific motif like a highly pathogenic bird influenza virus, it was shown that a reassortant virus possessing the 1918 HA gene inoculated into animals led to a severe inflammatory response and significant lung damage. This pointed to the HA gene of the 1918 viruses as a critical factor for its pathogenicity.

They also found that the viral RNA polymerase complex, viral enzymes necessary to ensure viral replication in the host, was a necessary virulent factor. The contemporary H1N1 virus is not detected in the lungs of infected animals. One of the distinguishing features of the 1918 virus was its ability to cause viral pneumonia. These studies showed that the recreated 1918 virus could replicate efficiently in the lungs of infected ferrets and non-human primates. It appears the RNA polymerase complex aids in the efficient spread of the virus to the lower respiratory tracts, and coupled with a specific HA, induces the type of fatal pneumonia encountered in the 1918-1919 pandemic.

The resurrected 1918 influenza virus is the virus from the second wave of the pandemic. Though the first wave caused extensive infection, it was not highly lethal. It is not known whether the virus in the first wave was the same as in the second wave or if it underwent a genetic shift or reassorted with another flu virus that made it so lethal. There is evidence that suggests those who developed the flu in the first wave had protection against the second wave. Medical workers, nurses, and doctors treating the wounded and infected soldiers also came down with the flu but demonstrated much lower mortality, indicating a protective benefit from possible exposure to the virus during the first wave.

The investigative work into the 1918 virus has enormous scientific interest. It also poses dangers. Under the control of military establishments and profit-driven healthcare corporations, the re-creation of a deadly virus could become the occasion for its development as a weapon of war, particularly if the disease can be targeted to specific populations through genetic engineering. It is hideous to contemplate, but there is little doubt that Pentagon planners envision a disease that disproportionately targets people of Chinese, Iranian or Arab ancestry, with (supposedly) less risk for those of European descent. Of course, given the power of mutation, such weapons would carry with them the prospect of the annihilation of humanity, just as surely as nuclear bombs. Even without the intervention of such biological Dr. Strangeloves, conditions in the world are rife with conflict and the dangers of a global war. Under such conditions, it is probable that pandemics may be a serious consequence, with food shortages, unsanitary conditions and lack of medical facilities all contributing. The destruction of Iraq in 2003, a nation with a population of 32.6 million people, has led to as much as one million deaths over a 15-year period, and this may be a conservative estimate. Sixty percent of these deaths were directly attributable to violence, with the rest due to the collapse of the infrastructure.

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