

# Why Was the 1918 Influenza So Deadly? An Intimate Debate Case

by  
Annie Prud'homme-Généreux and Carmen Petrick  
Life Sciences  
Quest University Canada

## Part I – The 1918 Influenza Pandemic

On September 29, 1918, an army physician stationed at Camp Devens, Massachusetts, wrote to his friend about a novel outbreak of influenza:

*Camp Devens is near Boston, and has about 50,000 men, or did have before this epidemic broke loose. It also has the Base Hospital for Div[ision] of the N[orth] East. This epidemic started about four weeks ago, and has developed so rapidly that the camp is demoralized and all ordinary work is held up till it has passed. All assemblages of soldiers taboo.*

*These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hospital they very rapidly develop the most vicious type of pneumonia that has ever been seen. Two hours after admission they have the mahogany spots over the cheek bones, and a few hours later you can begin to see the cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. (Roy as cited in Quinn, 2008, p.128–129).*

The 1918 influenza pandemic is estimated to have infected up to 500 million people (28% of the world's population) (Frost 1920; Burnet & Clark, 1942) and resulted in the death of 50 –100 million people (2.8–5.6% of the total world population) (Johnson & Mueller, 2002). In fact, there were more human casualties attributed to influenza than combat during World War I. Among Americans, the epidemic killed 675,000 people, including 43,000 servicemen (Crosby, 1989). There were so many deaths that the American life expectancy dropped by 10 years during the epidemic (Grove & Hetzel, 1968). While seasonal influenza usually kills approximately 0.1% of the victims it infects, the mortality rate of the 1918 influenza was greater than 2.5%, making the epidemic 25 times more deadly (Marks & Beatty 1976; Rosenau & Last, 1980). The 1918 “Spanish Influenza,” as it came to be called, killed 10 times as many Americans as did the 1957 Asian flu and 20 times as many as the 1968 Hong Kong influenza (Webster, 2001).

Was there something special about the biology of the 1918 influenza virus that made it particularly virulent and deadly? Or did the conditions in which people lived at the end of the First World War exacerbate a viral strain that would otherwise have been only mildly virulent? In this intimate debate, you will explore some of the evidence that points to a biological or a geopolitical-socioeconomic explanation for the devastation of the 1918 epidemic. Your goal is to understand these factors and to evaluate which are most likely to have affected the spread and severity of the 1918 influenza. You will be provided with a document containing a list of arguments for one side (biological or geopolitical-socioeconomic explanation for the pandemic's severity). Your goal is to understand the arguments, take notes, and soon after you will be responsible for teaching others about what you learned.

---

Photo of emergency hospital during influenza epidemic, Camp Funston, Kansas, 1918 (image NCP 1603 provided courtesy of the National Museum of Health and Medicine, Silver Spring, Md). The copyright for this case study is held by the [National Center for Case Study Teaching in Science](#), University at Buffalo, State University of New York. Originally published March 15, 2012. Please see our [usage guidelines](#), which outline our policy concerning permissible reproduction of this work.

## Team A

### *Geopolitical-Socioeconomic Explanation: Conditions Prevalent in 1918 Exacerbated the Effects of a Moderately Virulent Virus*

In November–December 1918, the United States Navy and Public Health Service conducted a series of experiments that argue that the 1918 influenza was not particularly transmissible or virulent. In these experiments, influenza was deliberately used to infect a group of 62 healthy volunteers<sup>1</sup> who had not been exposed to influenza that year (they should be immunologically naïve and susceptible to the virus). The researchers collected mucus from the nasal secretions of people afflicted with the flu and applied it to the nose, throat, and eyes of the test subjects. In another experiment, volunteers also had close contact for five minutes with patients who had begun to show flu symptoms less than three days prior (so they should still be shedding infectious agents). The interaction consisted of leaning over the sick patients, inhaling their breath, and chatting with them for five minutes. The sick patients then coughed in the volunteer’s face five times. Each volunteer repeated these steps with 10 sick patients. No volunteer reported symptoms of infection from any of these experiments. This experiment was later repeated with another group of 50 immunologically naïve volunteers put into close contact with infectious patients. Similar procedures were followed. Not a single man became sick (Rosenau et al., 1918; McCoy & Richey, 1921; Reported in Shope, 1958, and Kolata, 1999, p. 55–60).

In the late 1990s, almost a century after the initial epidemic, the 1918 influenza virus was recovered from preserved lung samples taken from American soldiers who died of the flu and from the lungs of a woman who was buried in the Alaskan permafrost following her death from influenza in 1918 (Taubenberger et al., 1997; Reid et al., 1999). This allowed researchers to examine the sequence of the genes that made up the 1918 influenza. The sequence of the 1918 HA and NA genes are discussed below.

- In influenza, one of the known virulence factors is a surface protein called hemagglutinin (HA). A number of different varieties of HA subtypes exist, all with slightly different mutations leading to different levels of pathogenicity. When the 1918 HA gene was sequenced, it did not contain any mutations known to cause exceptional virulence.
- The neuraminidase protein (NA) is another influenza surface protein that is a known virulence factor. NA cleaves sialic acid from the surface of new and emerging influenza virus particles, allowing the virus to escape the host cell and infect a new one. No mutation known to be associated with increased virulence was present in the 1918 influenza NA gene sequence.
- Sequencing of the 1918 influenza virus did not reveal any obvious reason why the virus might be virulent (e.g., mutations found in other strains known to be pathogenic).

As a result of the First World War, the health status of many people was less than optimal. This may have exacerbated the effects of a moderately virulent strain of influenza. Here is some evidence that supports the argument that the health of the population during wartime was compromised:

- “The medical situation in Europe was not the same in 1918 as it is today. The mortality from several infectious diseases was much higher (McKeon, 1976), and this cannot be explained only as a consequence of the absence of effective antibacterial drugs. Poverty was more prevalent than now, which had important consequences for the nutritional status of part of the population, and the argument has been made that the rapid decrease of childhood infectious disease in Europe during the period 1860–1970 may in large measure be explained by the improvement in nutritional status for a large fraction of the population that took place during this period” (Moxnes & Christophersen, 2008, p.4).
- Because the world had been at war for nearly four years, resources were extremely limited and were not being allocated to health care (Quinn, 2008, p.124). During armed conflicts, the displacement of populations, the breakdown in health and social services, and the heightened risk of disease transmission lead to negative health consequences (Murray et al., 2002).

---

<sup>1</sup> These volunteers were men convicted of crimes committed while at a U.S. Navy Training Station. Their crimes were pardoned in exchange for participation in the study. Today, research ethics boards ensure that such high incentives cannot be offered to inmates in exchange for participation in experimental research.

- Food production systems around the world had been disrupted by the war and large segments of the populations were under-nourished, and therefore had compromised immune systems (Moxnes & Christophersen, 2008; Quinn, 2008, p.126).
- Several pathogens are more lethal in hosts that are under-nourished compared to hosts that are well nourished (Leung et al., 2005; Christophersen & Haug, 2007). In particular, adequate selenium levels are needed to fend off influenza (Beck et al., 2001). In an experiment, mice were fed a diet that contained either adequate or inadequate levels of selenium. These mice were exposed to a strain of influenza that normally only causes mild symptoms. The selenium-deficient mice developed severe lung pathology, while the mice with an adequate level of selenium did not. In another experiment, it was discovered that selenium deficiencies in the host puts pressure on the influenza virus to mutate and consequently resulted in increased virulence (Nelson et al., 2001). Thus, nutritional deficiencies during WWI could have subdued the immune response to influenza, and in addition may have favored the evolution of a more virulent strain.
- Adequate levels of vitamin D are required to support a fully functioning immune system (Kankova et al., 1991; Cannell et al., 2008). In fact, lack of vitamin D during winter has been proposed as a contributing factor to explain why influenza affects humans mostly during winter months (Cannell et al., 2008). A lack of vitamin D during wartime may have weakened the immune system and contributed to the severity of the 1918 influenza pandemic.
- Many countries did not keep accurate mortality records during the 1918 pandemic. The mortality rates are estimated by extrapolating the death rates from the U.S., Western Europe, and Canada to the global population. However, there are suggestions that this leads to an underestimation. Studies propose a 30-fold greater death rate in India than in northern Europe (Murray et al., 2006). This has been attributed to the fact that conditions such as poverty are linked to higher death rates from the 1918 influenza.
- “The opportunity to give basic care has been shown to reduce mortality during historical influenza epidemics (Wolfe, 1982). There were reports of deaths from starvation and dehydration among aboriginals in Alaska (Crosby, 2003), Labrador (Graham-Cumming, 1967), Finland (Linnanmäki, 2006) and New Zealand (Pool, 1973; Rice, 2005) who may have survived the 1918–20 pandemic if the possible caregivers had not themselves also suffered high morbidity and mortality” (Mamelund, 2011, p.56).
- Twenty-four types of novel toxic gases (such as chlorine and phosgene) were used in battle during WWI. These gases left soldiers suffering from acute respiratory infections, which made them more vulnerable to viral respiratory attack (Erkoreka, 2009).

At the end of WWI, war efforts were the priority of governments. As a consequence, there was a lack of awareness, political will, and effective policies to contain and resolve the influenza epidemic. Here are a few examples of this mindset:

- American President Woodrow Wilson would not permit reports about the virulence of the outbreak to be published in the belief that it might weaken the war effort (Quinn, 2008, p. 125).
- The massing of troops caused unprecedented levels of overcrowding (for example, U.S. camps designed for 20,000 troops held twice that number) and the hospitals were not able to accommodate the extra soldiers (Quinn, 2008, p. 127).
- Troop ship movements were consistently carrying soldiers (symptomatic or asymptomatic) into virgin populations with no quarantines or preventative measures in effect (Quinn, 2008, p.136).

While the very young and young adults were at increased risk of death from the 1918 flu compared to seasonal flu, the elderly seemed to be at lower risk. It is hypothesized that the elderly who had survived the 1889 influenza epidemic had acquired immunity that protected them against the 1918 flu (Taubenberger et al., 2001). The immunity conferred by exposure to the 1889 influenza suggests that the 1918 virus may have borne similarities to the 1889 strain. The 1889 epidemic is not known to have been particularly virulent or deadly. This hints that other factors may have contributed to the lethality of the 1918 virus (Reid et al., 2001).



## Team B

### *Biological Explanation: The 1918 Influenza Strain was Exceptionally Virulent*

There were several influenza epidemics in 1918 that appeared in “waves” at the end of World War I (Mamelund, 2004, as cited in Moxnes & Christophersen, 2008). The first springtime epidemic (March–April 1918) spread rapidly and infected many people around the world, but caused relatively mild symptoms (low mortality). At the end of August 1918, a second wave started. This epidemic caused symptoms that were qualitatively and quantitatively different from the spring pandemic. While seasonal influenza normally targets the very young or the very old, young healthy adults were now also susceptible to this pandemic. Two thirds of the deaths caused by the “1918 influenza epidemic” occurred as a result of this strain of influenza during the months of October–December 1918. A third wave occurred around Christmas 1918 and lasted until March–April 1919. This pandemic did not spread to the same extent as the first one, and was not as lethal as the second one. Despite similar social and political conditions surrounding the three pandemics, the first and third waves caused mild symptoms, while the second wave caused severe and often lethal symptoms in the infected. This argues that the 1918 flu was devastating because of a particularly virulent strain of influenza, not the prevalent social or political conditions at the time.

In recent years, researchers successfully extracted 1918 influenza from lung samples taken from U.S. soldiers who died of the flu and whose tissues were preserved in paraffin (Taubenberger et al., 1997), as well as from the lungs of an infected woman whose body had been buried and preserved in Alaska permafrost (Reid et al., 1999). Laboratory animals were subjected to the recreated virus.

- The 1918 virus was “uniformly lethal in mice at low doses and produced severe lung pathology” (Memoli et al., 2009, p338). Mice infected with a recombinant 1918 flu had a much higher viral load and responded with enhanced inflammation and cell suicide responses (Tumpey et al., 2005; Kash et al., 2006). In ferrets, the 1918 flu caused severe lung pathology, very similar to the clinical symptoms reported for the 1918 flu in humans (Memoli et al., 2009). By comparison, seasonal flu caused little disease in either mice or ferrets. The exceptional pathogenicity of the recombinant 1918 flu was also observed in macaque monkeys, where the virus attacked cells found in the upper and lower respiratory tract (Kobasa et al., 2007). These observations echo reports of unusual 1918 flu pathology in humans. The seasonal flu typically attacks only cells in the upper respiratory tracts (Reid et al., 2001).
- To understand which genes of the 1918 influenza strain conferred exceptional virulence, researchers created hybrid influenza viruses containing seasonal flu genes in which select 1918 genes have been integrated. Mice infected with a virus containing the hemagglutinin (HA), neuraminidase (NA), or polymerase (PB1) gene from the 1918 virus had symptoms that were much more severe than the seasonal flu (Pappas et al., 2008). Mice infected with a virus in which the 1918 HA gene was present succumbed to the infection rapidly, had high viral loads, and the virus activated mouse genes involved in inflammation and immunity (Kobasa et al., 2004). Thus, the 1918 HA, NA, and PB1 genes appear to be critical components of the 1918 influenza virulence.

HA and NA are known virulence factors of influenza. Mutations in these genes can confer increased pathogenicity. Sequencing of the 1918 HA and NA genes revealed sequences that did not match any mutation currently known to increase pathogenicity (for example, mutations that make H5N1 influenza deadly) (Taubenberger et al., 1999). This does not mean that the 1918 virus does not encode a highly pathogenic virus. It is possible that the 1918 genes harbor novel mutations whose pathogenic effects are not recognized because they have not been observed or studied before. In addition, it is possible that pathogenicity is a polygenic trait (mutations occurring in several different genes lead to pathogenicity) (Reid et al., 2001).

Clinical descriptions of the 1918 influenza suggest a virus capable of replicating fast and spreading quickly from cell to cell. To achieve this, the 1918 strain would need to suppress the immune system. Emerging evidence suggests that two of the 1918 influenza proteins, PB1-F2 and NS1, can influence the activity of the host’s immune response.

- The sequence for a novel protein called PB1-F2 was recently discovered in the genome of influenza (Chen et al., 2001). This protein appears to induce apoptosis (cell suicide) and kill macrophages (immune cells), thereby

compromising the host's ability to produce an adequate immune response to the virus. The highly pathogenic Hong Kong 1997 H5N1 strain of influenza has an altered version of this gene, formed by a single point mutation (Conenello et al., 2007). An identical mutation was found in the 1918 flu PB1-F2 gene sequence. Mice infected with a seasonal flu virus containing this version of the PB1-F2 gene had decreased survival and 100-fold increase in viral replication compared to mice infected with the seasonal flu (Conenello et al., 2007). This suggests that the version of the PB1-F2 gene found in the 1918 virus contributes to the virus's pathogenicity.

- The NS1 protein from the 1918 virus appears to be an interferon inhibitor (Garcia-Sastre et al., 1998). Interferons are chemicals released by infected cells to warn neighbors of an impending viral infection. If NS1 is capable of antagonizing the interferon response, it would allow the influenza virus to escape this component of the innate immune response. A recombinant virus containing the 1918 NS1 gene sequence was more efficient at blocking the expression of interferon genes than the seasonal flu virus (Geiss et al., 2002)

Successful host infection requires the binding of HA to sialic acid receptors on the host's cell surface. HA proteins in avian strains preferentially bind to different receptor sites than human strains (Reid et al., 1999). Nonetheless, receptors preferred by avian strains are also present in the human lower respiratory tract, meaning humans can be infected by an avian influenza strain (Bouvier & Palese, 2008). The lower lungs are not as accessible to airborne pathogens as the upper respiratory tract, and therefore avian virus infection is rare in humans. However, when avian influenza strains infect the lower respiratory tract, a rapidly progressive and severe pneumonia can result (in clinical settings, fatality rates can exceed 60%) (Bouvier & Palese, 2008). Sequencing of the 1918 influenza reveals it to be avian in origin (Reid et al., 1999, 2000).

Seasonal influenza typically affects the very young and the very old. The influenza mortality curve (showing age groups on the X axis and mortality on the Y axis) is typically a U-shaped curve. This curve shape is usually attributed to the fact that young adults have better functioning and more robust immune system (so, therefore, a lower influenza mortality rate), while the young and elderly have less effective immune systems (with a higher mortality rate). If the 1918 influenza was a particularly virulent strain of the virus, the U-shaped curve might be expected to shift up, with all groups suffering more deaths uniformly. However, the 1918 influenza mortality curve is W-shaped, with a novel peak in mortality for young adults. Research suggests that a phenomenon called hypercytokinemia, or a cytokine storm occurred in young, healthy adults (Snelgrove et al., 2004; Osterholm, 2005). In a cytokine storm, the immune system overreacts to a foreign body, attacking host cells. The pathology of the 1918 flu suggested that the strain induced a cytokine storm in its victims (Harrison, 2010). The cytokine storm was lethal in the young healthy adults with highly functioning immune systems. The weak immune system of the very young and elderly afforded them some protection from the virus's effects. In fact, infection with the recreated 1918 virus caused the rapid onset of a cytokine storm in mice (Suresh & Kobasa, 2008). Therefore, it can be hypothesized that the healthy immune systems of young adults over-reacted to the 1918 flu, causing severe and potentially fatal symptoms.

In his book *Evolution of Infectious Diseases* (1996), Paul Ewald hypothesizes that through our actions we can favor the evolution of infectious agents that are either more or less pathogenic. According to this idea, in a given population of pathogens, there exists variability. Some organisms will cause severe symptoms in their hosts, while others will occasion only mild symptoms. If a pathogen needs its host to spread (i.e., it cannot be spread by vehicle or vector transmission such as by contaminated water), then the health status of the host will play a part in the spread. If a host is infected with a particularly virulent pathogen, then that host is incapacitated, and the spread is halted. If a host is infected with a mild form of the pathogen, then the host can continue functioning, is more likely to be in contact with other potential hosts, and the pathogen is more likely to spread and replicate. Therefore, natural selection will favor strains that only mildly affect the host. However, there was a potential reversal of conditions during World War I. If a soldier on the war front was infected with a mild form of influenza, he stayed on the war front, only contaminating others around him. However, soldiers who were infected with a particularly virulent form of influenza were removed from the trenches and transported in crowded troop trucks to crowded clinics or hospitals, giving the virus ample opportunities to infect many more hosts. Thus, the evolution of a virulent strain of influenza was favored, and this newly emerged pathogenic virus devastated the world (as reported in Gladwell, 1997).

## References

- Beck, M.A. et al. (2001). Selenium deficiency increases the pathology of an influenza virus infection. *FASEB J.* 15: 1481–1483.
- Bouvier, N.M., and Palese, P. (2008). The biology of influenza viruses. *Vaccine* 12 (26): D49–D53.
- Burnet, F., and Clark, E. (1942). *Influenza: A Survey of the Last 50 Years in the Light of Modern Work on the Virus of Epidemic Influenza*. Melbourne: MacMillan.
- Cannell, J.J., Zaslhoff, M., Garland, C.F., Scragg, R., and Giovannucci, E. (2008). On the epidemiology of influenza. *Virology Journal* 51–12.
- Chen, W., Calvo, P.A., Malide, D., Gibbs, J., Schubert, U., and Bacik, I, et al. (2001). A novel influenza A virus mitochondrial protein that induces cell death. *Nat Med* 7(12): 1306–12.
- Christophersen, O.A., and Haug, A. (2007). More about hypervirulent avian influenza: is the world now better prepared? *Microb Ecol Health Dis* 19: 78–121.
- Conenello, G.M., Zamarin, D., Perrone, L.A., Tumpey, T., and Palese, P. (2007). A single mutation in the PB1-F2 of H5N1 (HK/97) and 1918 influenza A viruses contributes to increased virulence. *PLoS Pathog* 3: e141.
- Crosby, A. (1989). *America's Forgotten Pandemic: The Influenza of 1918*. Cambridge University Press.
- Erkoreka, A. (2009). Origins of the Spanish Influenza pandemic (1918–1920) and its relation to the First World War. *J Mol Genet Med* 3(2): 190–194.
- Ewald, P.W. (1996). *Evolution of Infectious Disease*. Oxford University Press.
- Frost, W. (1920). Statistics of influenza morbidity. *Public Health Rep.* 35: 584–597.
- Garcia-Sastre, A., Egorov, A., Matassov, D., Brandt, S., Levy, D.E., Durbin, J.E., Palese, P., and Muster, T. (1998). Influenza A virus lacking the NS1 gene replicates in interferon-deficient systems. *Virology* 252: 324–330.
- Geiss, G.K., Salvatore, M., Tumpey, T.M., Carter, V.S., Wang, X., Basler, C.F., et al. (2002). Cellular transcriptional profiling in influenza A virus-infected lung epithelial cells: The role of the nonstructural NS1 protein in the evasion of the host innate defense and its potential contribution to pandemic influenza. *PNAS* 99(16): 10736–41.
- Gladwell, M. (1997). The dead zone. *New Yorker* (29 September 1997) 73(29): 52–65.
- Graham-Cumming, G. (1967). Health of the original Canadians, 1867–1967. *Med. Serv. J. Can.* 23: 115–167.
- Grove, R.D., and Hetzel, A. (1968). *Vital Statistics Rates in the United States: 1940–1960*. Washington, DC: US Government Printing Office.
- Harrison, C. (2010). Sepsis: Calming the cytokine storm. *Nature Reviews Drug Discovery* 9(5): 360–361
- Johnson, N.P.A.S., and Mueller, J. (2002). Updating the accounts: Global mortality of the 1918–1920 “Spanish” influenza pandemic. *Bull. Hist. Med.* 76: 105–115.
- Kankova, M. et al. (1991). Impairment of cytokine production in mice fed a vitamin D3-deficient diet. *Immunology* 72: 466–471.
- Kash, J.C., Tumpey, T.M., Prohl, S.C., Carter, V., Perwitasari, O., Thomas, M.J., Basler, C.F., Palese, P., Taubenberger, J.K., Garcia-Sastre, A., Swaine, D.E., and Katze, M.G. (2006). Genomic analysis of increased host immune and cell death responses induced by 1918 influenza virus. *Nature* 443(7111): 578–581.
- Kobasa, D., Takada, A., Shinya, K., Hatta, M., Halfmann, P., Theriault, S., et al (2004). Enhanced virulence of influenza A viruses with the haemagglutinin of the 1918 pandemic virus. *Nature* 431: 703–707.
- Kobasa, D., Jones, S.M., Shinya, K., Kash, J.C., Copps, J., Ebihara, H., et al. (2007). Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature* 445: 319–323
- Kolata, G. (1999). *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus That Caused It*. New York: Simon & Schuster.

- Leung, A.K., Kellner, J.D., and Davies, H.D. (2005). Rotavirus gastroenteritis. *Adv Ther.* 22: 476–87.
- Linnanmäki, E., 2006. Spanska sjukan i Finland. *Fin. Läkaresällsk. Handl.* 166 (1): 79–85.
- Mamelund, S-E, (2004). *Spanish Influenza and Beyond: The Case of Norway*. Dr. polit. Thesis, Department of Economics, University of Oslo, September 2004.
- Mamelund, S-E, (2011). Geography may explain adult mortality from the 1918–1920 influenza pandemic. *Epidemic* 2: 46–60.
- Marks, G., and Beatty, W.K (1976). *Epidemics*. New York: Scribner.
- McCoy, G.W., and Richey, DeW (1921). Experiments upon volunteers to determine the cause and mode of spread of influenza, San Francisco, November and December, 1918. *Hyg. Lab. Bull.* 123: 42.
- McKeon, T. (1976). *The Modern Rise of Population*. New York: Academic Press.
- Memoli, M.J., Tumpey, T.M., Jagger, B.W., Dugan, V.G., Sheng, Z-M, Qi, L. et al. (2009). An early “classical” swine H1N1 influenza virus shows similar pathogenicity to the 1918 pandemic virus in ferrets and mice. *Virology* 393(2): 338–345.
- Moxnes, J.F., and Christophersen, O.A. (2008). The Spanish flu as a worst case scenario? *Microbial Ecology in Health and Disease* 20: 1–26.
- Murray, C.J.L., King, G., Lopez, A.D., Tomijima, N., and Krug, E.G. (2002). Armed conflict as a public health problem. *BMJ* 324: 346–349.
- Murray, C.J.L., et al. (2006). Estimation of potential global pandemic influenza mortality or basis of vital registry data from the 1918–20 pandemic : Quantitative analysis. *The Lancet* 368 (9554): 2211–2218.
- Nelson, H.K. et al. (2001). Host nutritional selenium status as a driving force for influenza virus mutations. *FASEB J.* 15: 1846–1848
- Osterholm, M.T. (2005). Preparing for the next pandemic. *N Engl J Med* 352:1839–42.
- Pappas, C., Aguilar, P.V., Basler, C.F., Solorzano, A., Zeng, H., Perrone, L.A., Palese, P., Garcia-Sastre, A., Katz, J.M., and Tumpey, T.M. (2008). Single gene reassortants identify a critical role for PB1, HA, and NA in the high virulence of the 1918 pandemic influenza virus. *PNAS* 105(8):3064–9.
- Pool, I. (1973). The effects of the 1918 pandemic of influenza on the Maori population of New Zealand. *Bull. Hist. Med.* 47: 273–281.
- Quinn, T. (2008). *Flu: A Social History of Influenza*. London: New Holland Publishers (UK) Ltd.
- Reid, A.H., Fanning, T.G., Hultin, J.V., and Taubenberger, J.K. (1999). Origin and evolution of the 1918 “Spanish” influenza virus hemagglutinin gene. *PNAS* 96: 1651–1656.
- Reid, A.H., Fanning, T.G., Janczewski, T.A., and Taubenberger, J.K. (2000). Characterization of the 1918 “Spanish” influenza virus neuraminidase gene. *PNAS* 97(12): 6785–6790.
- Reid, A.H., Taubenberger, J.K., and Fanning, T.G. (2001). The 1918 Spanish influenza: integrating history and biology. *Microbes and Infection* 3: 81–87.
- Rice, G., (2005). *Black November. The 1918 Influenza Epidemic in New Zealand*. Canterbury University Press, Christchurch, NZ.
- Rosenau, M.J., Keegan, W.J., Goldberger, J., and Lake, G.C. (1921). Experiments upon volunteers to determine the cause and mode of spread of influenza, Boston, November and December, 1918. *Hyg. Lab. Bull.* 123: 5.
- Rosenau, M.J., and Last, J.M. (1980). *Maxcy-Rosenau Preventative Medicine and Public Health*. New York: Appleton-Century-Crofts.
- Shope, R.E. (1958). Influenza: History, epidemiology, and speculation. *RE Dyer Lecture* 73(2): 165–179.
- Snelgrove, R., Williams, A., Thorpe, C., and Hussell, T. (2004). Manipulation of immunity to and pathology of respiratory infections. *Expert Rev Anti Infect Ther* 2: 413–26.
- Suresh, M., and Kobasa, D. (2008). Pathogenicity of the 1918 pandemic influenza virus. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* 7(2): 81–86.

- Taubenberger, J.K., Reid, A.H., Krafft, A.E., Bijwaard, K.E., and Fanning, T.G. (1997). Initial genetic characterization of the 1918 “Spanish” influenza virus. *Science* 275: 1793–1796.
- Taubenberger, J. (1999). On the trail of history’s most lethal virus. *ASM News Issues* Vol. 65 July 99.
- Taubenberger, J.K., Reid, A.H., Janczewski, T.A., and Fanning, T.G. (2001). Integrating historical, clinical and molecular genetic data in order to explain the origin and virulence of the 1918 Spanish influenza virus. *Philos Trans R Soc London B* 356(1416): 1829–1839.
- Tumpey, T.M., Basler, C.F., Aguilar, P.V., Zeng, H., Solorzano, A., Swayne, D.E., Cox, N.J., Katz, J.M., Taubenberger, J.K., Palese, P., and Garcia-Sastre, A. (2005). Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* 310(5745): 77–80.
- Webster, R.G. (2001). A molecular whodunit. *Science* 293: 1773–1774.
- Wolfe, R.J. (1982). Alaska’s great sickness, 1900: Epidemic of measles and influenza in a virgin soil population. *Proc. Am. Philos. Soc.* CXXVI: 91–121.

