



Mini-review

THE AVIAN CONNECTION: THE 1918-1919 INFLUENZA PANDEMIC

James E. Hollenbeck*

Assistant Professor, Indiana University

247 Life Science Building, New Albany, IN 47150 USA

ABSTRACT

The focus of this paper was to examine the cause of this influenza outbreak and to explain its possible linkage to humans, since human beings live close to poultry and swine breeding facilities. This chain, in a way, poses a great risk of infection among humans. Animals act as reservoirs for this influenza virus and research indicates the influenza virus often originates in the intestines of the aquatic wildfowl. The virus is then shed into the environment where the domestic poultry gets infected. Subsequently this line of infection extends to mammals. The mammals in this chain, usually pigs, act as transformers or converters, creating a strain that can more readily infect humans. Therefore swine can be infected with both avian and human influenza A viruses and serve as a source of infection for a number of species, as the incidence of direct infection from birds to humans have been rare. It was this combination of environmental factors that may have contributed to the greatest pandemic of recent times.

Key words: Influenza, pandemic, epidemiology, Avian influenza, swine influenza, Spanish Influenza, vaccination.

INTRODUCTION

The casualty rate of the First World War was quite less than that experienced in the 1918-1919 Influenza Pandemic. Since then little progress has been made toward understanding the condition responsible for the extreme virulence of the "1918 type". Similarly, much has not been done toward unravelling the conditions necessary to prevent the reoccurrence of this epidemic. Unlike the typical "flu" that strikes the very young, chronically ill and the elderly, this flu would attack and kill healthy young adults. For example, Taubenberger (1), in a cohort study, reported that deaths resulting from the influenza and pneumonia among the 15-34-year-old were 20 times higher in 1918 than any previous time, and 99% of excess deaths among people under 65 years of age. This strain of influenza killed so many people that it reduced the life expectancy of the United States by ten years during its course. The

focus of this paper is to examine the cause of this influenza outbreak and explain why the linkage to the avian influenza is doubtful.

HISTORY OF THE DISEASE

The influenza virus is of animal origin and its infection of humans may date back as early as 2000 B.C.E. when humans began to domesticate animals. For example, Hippocrates described an epidemic with "flu-like" symptoms in 412 B.C.E. Subsequently Livy in ancient Rome described a similar outbreak of a sudden "malady" (2).

Early hypothesis of the origins of influenza occurrences were quite varied. Garret (3), in his contribution towards this, listed proposed factors that would initiate the onset of influenza to include "nakedness, dirt, unclean pyjamas, dust, open windows, closed windows, old books, fish contaminated by the Germans in 1918, Chinese people and cosmic influences". Other possible causes were attributed to "bad air", rotting corpses venting through the earth to rotten garbage in the streets. The primal source for all influenza "A" virus in mammals and domestic avian species is aquatic bird reservoirs.(4,5) The

*Correspondence to: James E. Hollenbeck,
Assistant Professor, Indiana University; 247 Life
Science Building; New Albany, IN, 47150 USA,
(812) 941-2360, jehollen@ius.edu

common denominator in every influenza outbreak is its ability to follow the travel routes from city to city and sicken large numbers quickly and killing the very young and the very old.

The association of avian influenza with the 1918 pandemic has not been determined; however, a more probable link still exists with the swine influenza. Oldstone (2) linked the 1918 reports and the observations of J.S. Koen, a veterinarian and inspector for the U.S. Bureau of Animal Industry in Fort Dodge, Iowa. He observed in pigs a disease that resembled the raging human influenza of 1918-1919. He noted as follows:

“Last fall and winter we were confronted with a new condition, if not a new disease. I believe that have as much to support this diagnosis in pigs, as the physicians have to support a similar diagnosis in man. The similarity of the epidemic among people and the epidemic in pigs was so close, the reports so frequent that an outbreak in the family would be followed immediately by an outbreak among the hogs, and vice versa, as to present a most striking coincidence if not suggesting a close relationship between the two conditions. It looked like the “flu” and until proven it was not the “flu,” I shall stand by that diagnosis” (2, 5).

Koen’s observations were unpopular at the time, especially among farmers raising pigs. Ten years later researchers with the U. S. Bureau of Animal Industry reported the successful transmission of influenza from pig to pig by infecting healthy pigs with mucus obtained from the upper respiratory tract of already infected pigs. Richard Shope, working with the Rockefeller Institute of Comparative Anatomy repeated the study and was able to reproduce the disease in healthy pigs with material taken from sick pigs and passed through a Pasteur-Chamberland filter. Shope provided the first evidence of virus transmitted by swine (2). In 1923, Richard Shope showed that people who were alive during the 1918-1919 epidemics had antibodies against the “pig” virus, but those born after 1920 lacked such antibodies (3).

According to Shope’s conclusion, which would be the dominant hypothesis, was that the source of the pandemic was an animal virus, which crossed from one species to another to eventually infect humans. Supporting Shope’s hypothesis of trans-species infection was an incident that occurred in an unrelated study in 1928. It involved canine distemper with ferrets being used as the study animals at the United Kingdom’s

Medical Research Council’s laboratory. Unexpectedly, the ferrets became ill with symptoms of human influenza, when one of the researchers became ill with the flu. Filtrate from washings obtained from the researcher’s throat was sprayed into healthy ferrets’ respiratory tracts. The ferrets became ill with the same symptoms (2). This provided the first evidence that a virus caused human influenza, and that it could be a trans-species virus thereby fulfilling Koch’s postulates on the transmission of the disease.

In 2002, when the first report of Severe Acute Respiratory Syndrome (SARS) emerged, influenza was thought to have been the culprit; however another zoonoses virus which jumped species from civit cats to humans would take the blame. After determining the exact sequence of the virus’s genome, which consisted of a 29,727-base-long strand of RNA, scientists were able to classify SARS as a corona virus (6). The corona virus family, which also includes the influenza virus, is split into three groups. One group infects birds, whereas the other two infect mammals. SARS was classified as a corona virus because it shares the same basic set of genes with other members of this family. Scientists found enough differences between SARS and other family members, to conclude that SARS represents a new fourth group. This means that SARS probably did not evolve from a previously known virus.

However, the Influenza viruses infect humans and a number of animals, most noticeably, swine and birds, which pose a greater threat than SARS. There are two major classes of influenza virus, type A and B. These two classes have similar structures, but all A virus proteins are different from B as far as their immunogenic potentials are concerned. Type A infects pigs, horses, seals, whales, and many types of birds as well as humans. This can be a trans-species virus.

Type B infects only humans (8). Animals act as reservoirs for this influenza virus and Gelbalt (7) indicated that the virus often originates in the intestines of aquatic wildfowl. The virus is shed into the environment, which in turn infects domestic poultry and finally to mammalian hosts. The mammals, usually pigs, act as a transformer or converters that are capable of creating a strain that can more readily infect humans. Pigs can be infected with both avian and human influenza A viruses. Human influenza H3N2 viruses have been detected in pigs in Asia, Europe, and Africa (10). These regions of the world such as Southeast Asia offer a close

environment, which is shared between fowls, pigs and humans. Some of these human and avian influenza viruses might become adapted to pigs and circulate in that population. The co-circulation of the viruses in swine, avian and human populations enhances the likelihood of genetic exchange, or “reassortment” of the genetic material

between these viruses. The mechanism of this reassortment or conversion is not understood, and has not been replicated in a lab. Nonetheless the probability of this process occurring is not to be dismissed casually. **Figure 1** depicts this interaction of how the virus may spread from one species to another.

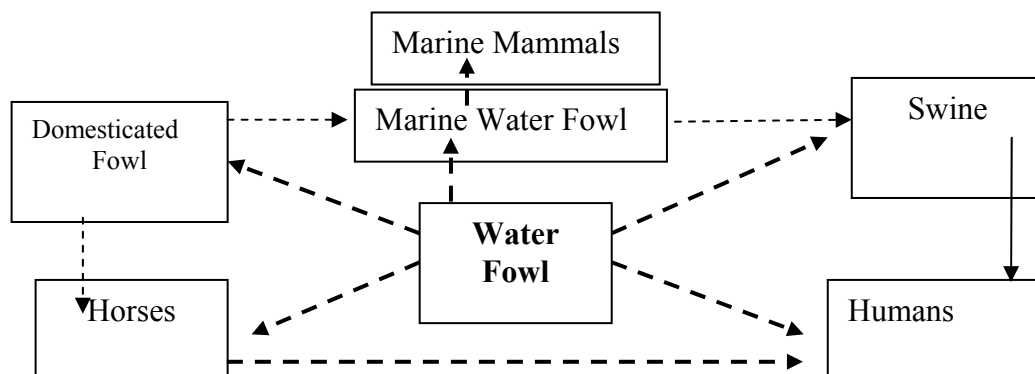


Figure 1: *The Reservoir of Influenza A Viruses* (10)

Wild Aquatic birds are believed to shed influenza “A” virus through their faecal wastes; other avian and mammal species readily pick up this virus from these wastes. Solid lines indicate known transmission to man from pigs and dashed lines show suspected inter-relationships.

With the difficulties of antigenic shift, drift, and animal reservoirs, it is not surprising that making an effective influenza vaccine is near impossible to achieve. Garrett (3) lists that the virulence of a virus is determined by: the efficiency of the haemagglutinin ability to drift; functional ability of the neuraminidase, and the immunological competence of the host. The first two factors are influenced by the genetics of the virus. The last factor is dependent on the health of the host to regulate a response to the virus. Garrett (3) reported that Dr. Edwin Kilburn, Mount Sinai School of Medicine in New York City has shown that influenza viruses unusually rich in neuraminidase proteins were more contagious and could take pieces of their host’s cellular membranes to help them evade the immunological responses of their host.

THE DISEASE

The onset of the 1918-1919 influenza pandemic occurred in three waves. The first wave, in the spring of 1918, was relatively mild, starting from the Midwest of the United States and spreading among soldiers located along the rail lines from Ft. Funston, Kansas, modern day Ft. Riley (3, 4). Patient zero was recorded cleaning pig pens prior to his

infection. There was no mention of the presence of poultry in the reports. From Ft. Funston the mild influenza spread to cities and other military bases throughout the United States. This mild strain received very little attention from the press; after all there was a war to occupy people’s attention. The spring outbreak was not even noted in the index in the 1918 volumes of the Journals of the American Medical Association. Influenza was not a reportable disease: the only evidence of the early occurrence was the registration of deaths reported as uncomplicated cases of pneumonia by physicians to various public health departments (11).

Medical researchers at the time offered the following hypothesis from what had happened to the influenza when it spread to France. The first theory was that this “Spanish flu” was actually a different disease. Decades later phylogenetic testing would find this to be false. Other theories implicated the following factors: the presence of gas warfare and chemicals used in explosives along with the number of corpses left unburied had created a new “super germ”. The potential of an airborne disease was enhanced because of the crowded conditions, closed-in living quarters with less hygienic conditions and rapid transport systems that allowed the ill individuals to pass the disease while in contagious stages (12). The crowded hospitals with hurried medical care procedures and mass transport of sick and dying soldiers, in their late teens and twenties, compounded the likelihood of an emerging infectious disease

or a possible mutation of an existing disease that would target this age group.

Those who had suffered from the earlier spring influenza generally suffered less discomfort in the fall outbreak. Despite the obvious differences between the strains, it was suggested that the more virulent form of influenza was genetically derived from the spring influenza (13). This cannot be proven and the antigenic composition of the 1918 virus is believed to be related to the H1N1 viral group. Phylogenetic studies have indicated that the virus responsible for the 1918 influenza and viruses that provided gene segments for the Asian/57 and Hong Kong/68 pandemics still circulate in wild birds, with few or no mutations (4). The extreme virulence of fall influenza strain has so far not been satisfactorily explained. Patterson and Pyle (13), Crosby (11) and many other researchers believe that a strain of pneumonia bacteria accompanied the virus. Noyes (15) noted that the nation's people were stricken and died from the illness at differing rates, just as the cities were hit at differing rates. There was no correlation between populations, or even geographical demographics. Sex and age both played a major factor in determining the susceptibility to the disease of the individual. Females were stricken in rates greater than males, and young adults were sickened in greater numbers than other age cohorts (14).

Climatic conditions may have had a role in the spread and severity of influenza. Cities in more harsh and cold climates tended to have somewhat lower death rates than those in more temperate climates (14). Most severe outbreaks would tend to occur during warm spells, followed by sudden drops in temperature. This trend was observed numerous times during the course of the epidemic.

THE GENETICS OF THE DISEASE

The virus is well protected by a tough lipid and protein coat made up of two layers of viral enveloping: one layer is composed of cholesterol, and the other layer of two proteins. These two proteins: hemagglutinin (HA) and neuraminidase (NA) are the two specific proteins recognised by antibodies. The two proteins are unique in structure and in function. Over 700 of these tiny spike-like proteins protrude from the envelope of the virus. Hemagglutinin grabs onto red blood cells in the victim, hitching rides throughout the body, and neuraminidase pinches and perforates the host's cells membranes.

Influenza types can be subdivided into subgroups according to the types of surface proteins located on the surface of their protein coats. Presently, 15 different H and 9 different N antigens have been identified. Type A influenza viruses are made up of various combinations of H and N antigens but only a few of these combinations, H1N1, H2N2, H3N2 and H5N1, have been found to cause human illness (6). However, other H and N virus combinations have been found in other infected animals.

A change in the NA amino acid sequence may allow a "back-door" to HA cleavage, leading to systemic infection. This mutant NA will bind to plasminogen, a normal precursor in the blood clotting system. If plasminogen is converted to plasmin, the active form, it functions as a protease to cleave HA which creates a systemic infection as well (1). Taubenberger (1) reported that this transformation was not observed in the 1918 strain or in strains "captured" in nature.

The influenza virus is changing all the time. Major antigenic "shifts" occur in influenza type A, creating the emergence of new flu viruses. The virus undergoes a series of small changes in the NA and HA proteins called "drift." Experiments have demonstrated that drift results from mutations in the pieces of RNA coding for hemagglutinin and neuraminidase. These cause small alterations in the regions (epitopes) on the NA and HA molecules that bind antibodies to the viruses (2, 7). This mutation permits the viruses to "escape" and infect the victim, who might be previously immune.

Three major hypotheses have been offered by Oldstone (2) to explain antigenic shifts:

- A new virus can come forth from a re-assortment in which an avian virus gene is substituted for one of the human influenza virus genes.
- Viruses that infect other birds and mammals become infectious to humans. This is the commonly accepted explanation of the 1918-1919 Pandemic.
- The newly emerging virus has actually remained hidden and unchanged somewhere but suddenly came forth to cause an epidemic against an unprotected population with little or no immunity.

The influenza virus is able to initiate these shifts because it follows an evolutionary process of natural selection that acts in a method called "positive selection". This allows the codons in the HA genes to change. Researchers have ample evidence to trace the

non-silent mutations of the influenza virus amino acid as the strains that show the greatest numbers of mutations are more likely to be progenitors for future generations of the virus (15). Knowing this, we may be able to predict which strains may likely become the progenitors for future strains in future outbreaks. The predictor for the future strains rests with ability of the codons to combine with antibodies, and associate with sialic acid receptor binding sites of the antibodies.

The work of Fitch et. al (6, 15) was utilised by researchers at the St. Jude Children's Research Hospital in Memphis, Tennessee studying the 1983 avian flu virus before and after it became virulent. They discovered that a single base change in the RNA segment coding the HA spike caused a single amino acid sequence in the hemagglutinin to produce a killer virus. This drift occurs in both types A and B; the major shifts, however, occur in type A. This may be due to the factor of the multiple host/reservoirs for type A as shown on **Figure 1**. However the likelihood of the avian influenza being the direct cause of the 1918 Influenza Pandemic is not very plausible. Prior to the 1997 H5N1 outbreak in Hong Kong, avian influenza was reported rarely and was believed to be highly restrictive (16). There is no evidence that the H5N1 virus has been adapted to humans. Influenza virus is protein specific to their binding sites and humans and birds lack a common sialic acid receptor on host cells. In order for the avian influenza virus to infect humans, domestic pigs must act as immediate hosts and "mix" or "convert" the virus to a human virus (17). This hypothesis is consistent with the observation that many pandemics occur in areas where duck, swine and humans are in close contact. The role of swine as a converter is still not completely understood.

The evidence for direct human infection by fowl is not strong and considering that the influenza virus is shed through their faeces makes proof of human infection even more difficult. The case against swine in transmitting the avian influenza is not proven either. One, how does an intestinal virus change to that of a respiratory airborne-virus that is adapted to the mammalian lung? Second, the viruses must adapt to environmental changes, able to withstand temperate, moisture and pH changes. Finally, the surface proteins as discussed earlier must be adapted.

CONTROL OF THE DISEASE

Presently, the only effective measure we have to combat influenza is isolation and culling of infected fowls as demonstrated by the governments of China, Vietnam, and Thailand. As human populations continue to increase and interactions between animals and humans become more proximate, the emergence of new influenza strains will occur (10, 18). Traditionally pigs will continue to be reared along poultry in densely settled rural regions. Agricultural reforms in China are moving pigs away human living quarters (4). In the United States this practice is being reversed as the animal industry continues to develop highly dense animal population feed lot concepts for raising swine and poultry near populated regions. In areas that are climatically similar to southern China, the conditions of mixing humans, aquatic birds, poultry and swine provide excellent conditions for interspecies transfer and genetic exchange among influenza viruses (5). Robert Webster of the St. Jude's Children Hospital of Memphis concluded that all the genes of influenza reside in the world's population of aquatic birds, in ducks and gulls, and are periodically transmitted to pigs and humans (19). Pigs act as the "transformers or converters" for the various influenza viruses and let loose to the world new "strains" of the influenza virus. The intervening passage continues to be through the domesticated pig. The genetic structure of influenza continues to be unstable and many different influenza "A" strains can exchange subunits of DNA to produce numerous sub-strains. Generally these new combinations are minor, with few virulent strains emerging.

Until we gain control of this continuous reshuffling of genetic material the annual "flu shot" is the best preventive strategy for the elderly and chronically ill. A chemically produced vaccine is 30-70% effective in increasing the resistance to influenza. The advantage of the vaccine is that it decreases the severity of the virus, reducing the side effects and complications of an influenza attack. Antigenic shifts and drifts with numerous reservoirs make the development of a universal and long-term vaccine unlikely. Laver, Bischofberger and Webster (8) are doubtful that influenza vaccines will ever be able to cope with the mutability of the vaccine. Time to research, develop, safety-test and distribute the vaccines is enormous. They advocate the development of anti-viral drugs similar to antibiotics used for bacterial infections.

The anti-viral drugs recently developed

bring concerns of the development of drug-resistance viruses. They must be administered before the infection or shortly after the first symptoms appear, generally within the first 48 hours (20). Finally an important concern involves misdiagnosis of other viral diseases and bacterial infections that may be mistaken for the “flu”.

The question about when the next influenza pandemic will occur still remains. Every influenza pandemic, since 1850 (other than the 1918 pandemic) has originated in China (4). The H2 Eurasian virus originating in Southeast Asia may be the next precursor of a future human pandemic. Webster (4) has recommended that the frequency of H2 isolates in aquatic birds, pigs and humans be carefully monitored. Live animal markets are areas of grave concern as these areas may provide vital sentinel sites for the emergence of new strains of influenza. We have witnessed two such mild pandemics in recent history since 1918-1919; the 1957 Asian flu and 1968 Hong Kong flu were such examples. No doubt, humanity remains vulnerable to any future pandemic.

REFERENCE

1. Taubenberger, Jeffery. “On the Trail of History’s Most Lethal Virus” *ASM News Issues*. Vol. 65 (7). July, 1999.
2. Oldstone, Michael, B.A. *Viruses, Plaques and History*. Oxford University Press, NY, NY. (1998).
3. Koen, J. S. “A Practical Method for Field Diagnosis of Swine Disease” *American Journal of Veterinarian Medicine*. 14(1919):468
4. Webster, R.G. “Predictions for Future Human Influenza Pandemics”. *The Journal of Infectious Diseases*. 1997:176(Suppl 1)S14-19, (1997).
5. Webster, R.G., Bean, WJ, Gorman OT, Chambers TM, Kawaoka Y, “Evolution and Ecology of Influenza A viruses”. *Microbiology Review*, 56:152-79, (1992).
6. Garrett, Laurie. *The Coming Plaque*. Harper Collins, NY, NY. (1994).
7. Mendoza, M. “SARS: The First New Virus of the 21st Century”. Educational Resources Development Council, University of Utah, (2004).
8. Laver, W. G., Bischofberger, N., and Webster, R.G. The Origin and Control of Pandemic Influenza. *Perspectives in Biology and Medicine*. Vol. 43(2) Winter 2000.
9. Gelbart, Marsh. Influenza: The Mutating Assassin Waiting to Strike. *Nursing Times*. Vol. 95(45) Nov. 10, 1999.
10. Virus Weekly. *Implications of H5N1 Infections in Pigs in China*. September 21, 2004.
11. Cosby, Alfred. *America’s Forgotten Pandemic, The Influenza of 1918*. Cambridge University Press, NY, NY. (1989)
12. Ewald, Paul W. *Evolution of Infectious Disease*. Oxford University Press, NY, NY (1994)
13. Patterson, K. D and Pyle, F.G. The Geography and Mortality of the 1918 Influenza Pandemic. *Bulletin of the History of Medicine*, vol. 65:(4-12) 1991.
14. Noyes, William R. Influenza Epidemic 1918-1919: *A Misplaced Chapter in the United States Social and Institutional History. An unpublished dissertation*. University of California-Los Angeles, CA. (1968)
15. Fitch, W.M., Bush, C.A., Bender, K., Subbarao, K. and Cox, N.J., “Predicting the Evolution of Human Influenza A” *The American Genetic Association*. 91:183-185. 2000
16. Bush, R. M. “Influenza as a Model System for Studying the Cross-Species Transfer and Evolution of the SARS Coronaral Virus”. *Philosophica Transactions of the Royal Society of London*. Published online June 2, 2004.
17. Scholtissek, C. “Pigs as ‘Mixing Vessels’ for the Creation of New Pandemic Influenza Viruses”. *Medical Principles Practice*. Vol. 2. 65-71. (1990).
18. McMichael, A.J. “Environmental and Social Influences on Emerging Infections Diseases: Past, Present and Future”. *Philosophica Transactions of the Royal Society of London*. Vol. 359, pages 1049-1058. (2004)
19. Taubenberger, J. Reid, A. Kraft, A. “Initial Genetic Characterization of the 1918 “Spanish” Influenza Virus”. *Science* 1997; 275:1793-6.
20. Hollenbeck “The 1918-1919 Influenza Pandemic: A Pale Horse Rides Home from War” *Bios*. 73:Nov.1, 2002.