

Short research communication

An Avian Connection as a Catalyst to the 1918-1919 Influenza Pandemic

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The 1918 Influenza pandemic was one of the most virulent strains of influenza in history. This strain quickly dispatched previously held theories on influenza. World War One introduced new environmental stresses and speed of dissemination logistics never experienced by humans. In light of new phylogenetic evidence the cause of this influenza outbreak is now being considered to have linkage to the avian influenza. Animals act as reservoirs for this influenza virus and research indicates the influenza virus often originates in the intestines of aquatic wildfowl. The virus is shed into the environment, which in turn infects domestic poultry, which in turn infects mammalian hosts. These animals, usually pigs, act as a transformer 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 for infection for a number of species as the incidents of direct infection from birds to humans have been rare. Increased human habitation near poultry and swine raising facilities pose greater influenza outbreak risk. It was this combination of environmental factors that may have contributed to the greatest pandemic of recent times, and, moreover, similar conditions exist throughout Southeast Asia today.

Key words: Influenza, pandemic, epidemiology, avian influenza, swine influenza, Spanish Influenza, vaccination

1. Introduction

The death toll of the First World War failed to inflict the human casualty rate that the 1918-1919 Influenza Pandemic did. Little progress has yet been made toward understanding the condition responsible for the extreme virulence of the "1918 type", and or the conditions necessary to prevent the reappearance of this influenza. Unlike the typical "flu" that strikes the very young, chronically ill and elderly; this flu would attack and kill healthy young adults. Taubenberger [1] that reported deaths resulting from the influenza and pneumonia for the 15-34-year-old cohort was 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 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.

2. 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. Hippocrates described an epidemic with "flu-like" symptoms in 412 B.C.E and later 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] lists proposed factors that would initiate the onset of influenza to include "nakedness, dirt, unclean pajamas, 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 common denominator in every influenza outbreak was its ability to follow the travel routes from city to city and sicken large numbers quickly and killing the very young and 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] link 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:

"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, 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 taking mucus from the secretions from the upper respiratory tract of infected pigs to healthy 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, 6].

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 an incident occurred in an unrelated study in 1928, of 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. Washings were obtained from the researcher’s throat and sprayed the filtrate into healthy ferrets’ respiratory tracts. The ferrets became ill with the same symptoms [2, 5]. This provided the first evidence that a virus caused human influenza, and that it could be a trans-species virus fulfilling Koch’s postulates on the transmission disease.

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 the immune system is 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] cited research that indicates the virus often originates in the intestines of aquatic wildfowl. The virus is shed into the environment, which in turns infects domestic poultry, which in turn infects mammalian hosts. These animals, usually pigs, act as a transformer or converters; creating a strain that can more readily infect humans. Pigs can be infected with both avian and human influenza A viruses. Human influenza viruses have been detected in pigs in Asia, Europe, and Africa [10]. 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 it 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. None the less the probability of this process is not to be dismissed casually.

Wild Aquatic birds are believed to shed influenza “A” virus through their fecal wastes, which is readily picked up by other avian and mammal species. Water fowl are believed to be the source of many of the influenza viruses and are responsible for their re-emergence prior to pandemics [8, 12, 20].

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 the virulence of a virus is determined by: the efficiency of the hemagglutinin ability to drift; functional ability of the neuraminidase, and the immunity of the host it infects to fight the virus. 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 was

able to take pieces of their host’s cellular membranes to allow them to evade the immunological responses of their host.

3. The 1918-1919 Pandemic

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 and spreading along the rail lines with soldiers from Ft. Funston, Kansas, modern day Ft. Riley. [3, 4] Patient zero was recorded cleaning pig pens prior to his infection. There is 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 what had happen to the influenza when it went to France. The first theory that was offered was that this “Spanish flu” was actually a different disease. Decades later phylogenetic testing will find this to be false. Other theories were that 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 is 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 indicate that the virus responsible for the 1918 influenza and viruses that provided gene segments for the Asian/57 and Hong Kong/68 pandemics are still circulating in wild birds, with few or no mutations [4]. The extreme virulence of fall influenza strain has so far not been satisfactory explained. Patterson, K. D., and Pyle, F. G. [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.

4. The Genetics of the Disease

Unlike most viruses, the influenza virus may exist in many different shapes. The virus is well protected by a tough lipid coat made up of two layers of viral enveloping: one layer is composed of cholesterol, and the other layer of two proteins: hemagglutinin [HA] and neuraminidase [NA]. Both proteins are recognized 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 will attach on the cell membranes through receptors on the cell, containing sialic acid and fuse on the membrane, allowing the RNA of the virus to enter the host cell. The neuraminidase removes the sialic acid receptors from the host cell membrane and from newly made viruses which enable the virus to continue to infect other cells if neuraminidase is blocked the viruses "clump" together on cell surfaces and are unable to complete their cycle [8].

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, 8]. However, other H and N virus combinations have been found in other infected animals.

A change in the NA amino 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 of 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, 8]. 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 come forth to cause an epidemic against an unprotected population with little to 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 the progenitors for future generations of the virus [15]. Knowing this we may be able to predict which strains may be likely to be the progenitors for future strains in future outbreaks. The predictor for the future strains rest 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 utilized 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. 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 [6, 14].

The evidence for direct human infection by fowl is not strong and considering that the influenza virus is shed through their feces makes prove of human infection even more difficult to prove. 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 prior must be adapted.

5. 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 government 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, 8]. Robert Webster, M.D. of the St. Jude's Children Hospital of Memphis, has 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 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.

The question when will the next influenza pandemic occur still remains? Every influenza pandemic since 1850, [other than the 1918 pandemic] has originated in China [4, 8, 15]. With the recent occurrences of the new "bird" influenza and the accidental release of the 1957 H2N2 influenza strains to labs, time may be running short until the next pandemic.

Conflict of interest

The author has declared that no conflict of interest exists.

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