

The 1918 Spanish Flu Pandemic, the Origins of the H1N1-virus Strain, a Glance in History

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Abstract: It was the year 1918, when a new flu pandemic launched worldwide. Our study purports to depict the general icon of the 1918 pandemic epoch, for the readers to shape an overview of the events of the era. We have used some of the most important manuscripts concerning the pandemic to compose a historical note on the outbreak that almost annihilated the world. The name “Spanish Flu”, was defined wrongfully due to the scientific observation and research made in Spain, while the first appearance of the virus had been made in USA. The outbreak was devastating, causing millions to die, more than the First World War casualties. During new experiments upon the old virus strain, it was proved that the 1918 pandemic was caused by an influenza A - subtype H1N1 progenitor strain. Our mini review, enlightens some aspects of virus blast, in an effort for the readers to luxuriate in the tale, myths, and the true story of the 1918 pandemic.

Keywords: 1918, Spanish Flu, Influenza A, H1N1, Pandemic, History of Medicine

1. Introduction

The majority of all human infectious diseases and pandemics have originated through the cross-species transmission of microorganisms from animals to humans, and vice versa. The influenza A virus, eloquently illustrated how our global interconnectedness can affect the worldwide distribution of a new virus, or virus strain, one that may otherwise have remained a regional phenomena in an era before the globalized world [1]. A thorough reopening of the history archives will demonstrate the fact that most of the worldwide spread pandemics had their point zero in the continental Asia, and Africa from where they had spread to rest of the world. The three great plague pandemics had different geographic origins and paths of spread. The Justinian Plague of the 541 AD, started in central Africa and spread to Egypt and the Mediterranean. The Black Death of the 1347 AD, originated in Asia and spread to the Crimea then to Europe and Russia. The third pandemic, that of the 1894 AD, originated in Yunnan, China, and spread to Hong Kong and India, then to the rest of the world [2]. During 1918, a flu

pandemic deviated from this axiom. Our study aims to create a mini review for the inside story of the 1918 pandemic for the readers to form a general conception for the era.

The 1918 pandemic, an influenza that engulfed nearly every part of the world, known also as the “*Spanish Flu*”, was firstly appeared in the USA and in April of the same year in a British constitution in a French city called Rouen, where it has been called “*La Grippe*”. During 1918, Europe was devastated by the First World War, and Spain as a neutral country had all the time to deal with the disease and its consequences and claim the name. Hence the most reliable scientific facts for the disease came from Spain, giving the international community the false impression that Spain was the most affected zone. The flu had travelled alongside with the military forces in the entire France and from there to the rest of Europe, closing its loop in the USA [3-5].

The pandemic infected 3% to 5% percent of the world's population including remote Pacific islands and the Arctic. The Life expectancy dropped by about 12 years. The British scientific team led by virologist John Oxford of “Saint Bartholomew's Hospital”, investigated thoroughly the first

wave, identifying the major troop staging and hospital camp in a commune in the Pas-de-Calais department in northern France, the Étaples, as almost certainly being the centre of the 1918 influenza pandemic. The deadliest virus spread began, terrifying the whole world, killing previously healthy young adults [6-7].

2. The Spanish Flu pandemic

It was the fifth year of the World War I, when the influenza pandemic had been widespread from America to all over Europe, presenting an especially virulent influenza pandemic struck [Figure 1]. The pandemic hit an unprepared and suffering part of the world in three consecutive waves during spring, fall and winter in a period of twelve months. Despite the fact that the flu had also appeared in India, in New Zealand and in South Africa, the dominant impression was that it mainly concerned Europe, Asia and North America. A peculiar oddity was that the virus dispersion happened worldwide during the summer and autumn, as influenza is usually worsens during the winter time. The second vague appeared during September to October of 1918 and spread again geometrically, but this time only Australia remained unaffected and that until 1919 [8-11]. Yet, the first wave of the flu had largely gone unnoticed in the spring and summer of 1918. The spring wave did not even receive a mention in the index of 1918 volume of the journal of *"The American Medical Association"*. The disease at the beginning had been mild, the mortality was not unusually high, and the world had been preoccupied with the events of the war. However influenza was brewing quietly, with localized outbreaks inside the U.S. military camps in early 1918. By April the disease had spread to France, most probably carried there by the American troops [Figure 2]. In the United States, the disease was first observed in Haskell County in Kansas, spreading further towards Canada and Alaska, where entire communities were perished. India, Indonesia, Samoa, Japan, Ethiopia, and South Africa were hit too [Figure 3 & Figure 4]. At the end of April influenza did reach neutral Spain where the disease was widely publicized, *"A strange form of disease of epidemic character has appeared in Madrid"*, as written during that era. Influenza then, acquired its spurious name, *"The Spanish Flu"* [Figure 5]. In Spain thaw, a different nickname was adopted, a name that came from a musical operetta (zarzuela) titled *"La canción del olvido"* (The Song of Forgetting), which premiered in Madrid during the first epidemic wave. Spanish poet and essayist Federico Romero (1886-1976), one of the librettists, quipped that the play's most popular musical number, *"Naples Soldier"*, was as catchy as the flu. Influenza acquired its new nickname, the *"Naples Soldier"* flu (Soldado de Nápoles) [11]. Britain, Germany, Switzerland, and Poland were the next countries for the flu to be transmitted [Figure 6]. By May, *"Spanish flu"* had reached Greece [3, 12-13].

In Greece, on July 19th of the year 1918, in an article entitled *"Spanish flu"*, appeared the first recorded reference for the appearance of the influenza pandemic in Greece. It was at the Peloponnesian town of Patra, where a few days

earlier, a flu outbreak had shown its malignant character. Physicians of the era had recognized the flu's similarity to that which had been occurred in Spain. On October the 6th *"Thessalia Newspaper"* [Greek: Θεσσαλία] published the whole telegram from the *"Hellenic Ministry of Internal Affairs"*, which depicted the European scientific knowledge of the era, *"The disease germs enter the body through the mouth, and generally from the respiratory system. Frequent gargles, mainly with an oxygenated water and antiseptic cream, may have some preventive action. The disease spreads by coughs and transmitted by air. Therefore it is recommended the avoidance of mentally stress and overwork, as well as concentrations of each kind. All schools must be close, and meticulous maintenance of cleanliness of lingerie and hands is proposed. In particular, it is highly recommended to avoid close contact with every person who displays flu symptoms"* [12]. Objects that were constantly being used by the sick people, like tickets in the tramways, pencils at schools, blankets at hospitals, or in the army, even the holy water in the churches, were also considered as means of transmission. It was the mayor of the French city of Lyon Eduard Herriot (1872-1957), who had firstly understood the significance of the public hygiene and took some effective measures to face its extreme contagiousness. Thus, by functioning as a kind of one-man sanitary squad, to keep deaths to the minimum, he disinfected the tramways, forbade the public gatherings and even the funeral processions, he had organised a system of rapid burials, while the holy water should be mixed with antiseptics for the protection of believers. Worldwide The public health departments distributed gauze masks to be worn in public [Figure 7 & Figure 8], while hospitals embrace the *"fresh air cure"* for the new virus, by simply arranging beds or tents outside the main builds [Figure 9] [14].

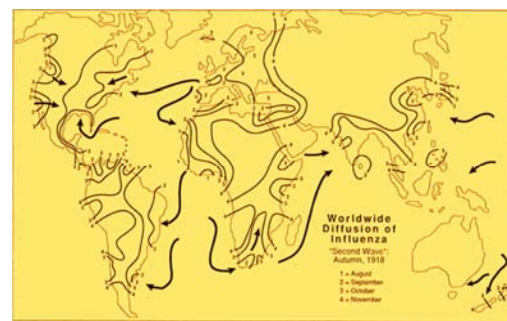


Figure 1. Map depicting the Spanish flu pandemic 1918, Patterson KD, Pyle GF. The geography and mortality of the 1918 influenza pandemic. *Bulletin of the history of medicine*, 1991; 65(1): 4-21.



Figure 2. A pneumonia porch at the US army Hospital in Aix-les-Bains, France, 1918. Influenza ward at Walter Reed Hospital, in Washington, D.C. during the Spanish flu pandemic of 1918-1919.

rate of 0.1% [17]. The fatal casualties of the diseased had reached the number of the fifty million victims [18], (France: 100.000 deaths, England: 220.000, USA: 550.000), more than the entire number of the victims of the First World War [19]! Even in areas where mortality was rather low, a significant percentage of the general population was incapacitated, resulting much of everyday activity to be hampered. In some communities the majority of the stores were closed, or the owners required customers to postpone, or leave their orders outside the shops. An influenza-phobia was spread among the common people. This pandemic had been described as “the greatest medical holocaust in history” and may have killed more people than the Black Death, caused by the bubonic plague [20].

A unique feature of this pandemic was that it mostly killed young adults, while 99% of the deaths occurred in inflicted aged under 65 years old, with more than half concerning the diseased between 20 to 40 years of age. This was an unusual distribution, since influenza was, and in fact is, normally deadlier among the very young, aged under 2 and the very old, aged over 70, and milder among the patients in their prime. The fact that the sensitive fractions of the population have had a better immune response could be explained by the partial protection due to their exposure to the previous Russian flu pandemic of the 1889 [Figure 11] [21]. In fast progressing cases death was occurred primarily due to virus-induced pneumonia, while the slower progressing diseased had featured secondary bacterial pneumonias. In many patients neural involvement led to mental disorders, which were appeared [5]. Both morbidity and mortality were unusually high [3]. Some deaths were the result of malnutrition and famine due to the war [15], while a great number were resulted due to the overdose of the aspirin drug [22].

Unfortunately the two year Spanish flu pandemic deprived the life of some important members of the affected communities, such as Guillaume Apollinaire, French poet (November 9, 1918), Max Weber, German political economist and sociologist (June 14, 1920), Larry Chappell, American baseball player, (November 8, 1918), Sophie Halberstadt-Freud, daughter of Austrian psychoanalyst Sigmund Freud, (1920) and Edmond Rostand, French dramatist, best known for his play *Cyrano de Bergerac*, (December 2, 1918), while Joseph Joffre, French World War I general, and Franklin D. Roosevelt, American president, survived the infection [23].

Scientists, recent years, somewhere between 1996 and 2005, have used tissue samples from deep frozen victims to reproduce the virus strain for a thorough study. Not everyone was so enamored of the Frankenstein-like experiment on such a lethal viral monster but it provided some valuable historical information [3]. The researchers have concluded that the virus binds with its HA-protein towards sialic acid receptors on host cell surface and kills it via a cytokine storm [24], a bond that explains its unusually severe nature and the concentrated age profile of its victims.

The Spanish flu pandemic during 1918 was caused by an unusually virulent and deadly influenza A virus strain of the subtype H1N1. Modern analysis has proved the virus to be particularly deadly, as it triggers a cytokine storm, which ravages the stronger immune system of young adults, causing death waves among them. On the other side, many researches suggested that as the samples survived, were all from patients of the second wave, when the virus re-emerged in an extremely virulent fashion, we may not be certain of the first wave's virus strain, and that could be a progenitor of the H5N1 subtype [17]. Phylogenetic analyses suggest that the 1918 virus HA gene, although more closely related to avian strains than any other mammalian sequence, is mammalian and may have been adapting in humans before 1918. Of all mammalian H1s, those of the 1918 viruses are most similar to their avian counterparts. However, the 1918 HA-virus gene has accumulated enough non-selected, mammal-associated changes to place it consistently in the mammalian clade phylogenetically. Swine were the first animals to present the disease during 1918 [25]. Nevertheless it was an influenza A pandemic [17, 25].

In 1918 the French bacteriologist Charles Nicole (1866-1936) [Figure 12], had came to the conclusion that the strain originated in a mammalian species. Alongside with his colleague Lebailly C, came to the conclusion that the cause of the flu had to be a virus that can be filtrated. The real etiologic factors of the flu, the viruses of the “*Orthomyxoviridae*” family, were identified by Richard Edwin Schope (1901-1966) [Figure 13] in swine, during 1931 [10, 26]. This significant discovery was followed by the isolation of the human virus by the British virologist Patrick Playfair Laidlaw (1881–1940) [Figure 13] and his colleagues, during 1933, before George Keble Hirst (1909-1994), the famous American virologist, in 1941 was finally able to understand an important ability for the study of the virus, the haemagglutination [27]. Meanwhile it was in 1933, when the use of the newly electronic microscopes that allowed the virus to be visible, while during 1935 Frank Macfarlane Burnet (1899-1985) [Figure 12], cultivated the virus inside a chicken egg. This progenitor of the modern H1N1 virus had evolved with unremitting mutations leading the medical community to a cursive battle against the mutated influenza virus-A [10].



Figure 10. American nurses of the “Red Cross”, ready to intervene for recovering patients.

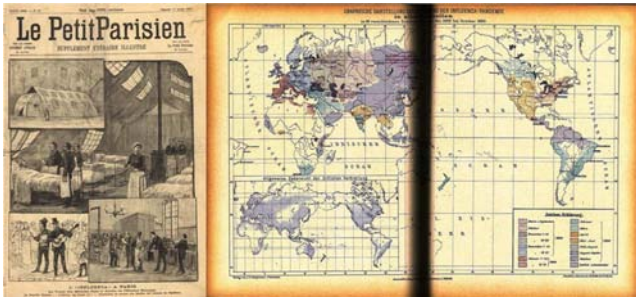


Figure 11. The front page of the “Petit Parisien” newspaper including 4 illustrations of a medical tent in the Parisian Hospital Beaujon, “La Tende des Malades dans le Jardin de l’Hôpital Beaujon”, 1890 (left side). A map depicting the Russian flu pandemic, Graphische Darstellung Des Auftretens Der Insuenza-Pandemie In allen Erdtheilen in 16 verschiedenen Zeitaltschnitten, von Mai 1889 bis October 1890 (right side).



Figure 12. Charles Nicole at microscope, Pasteur Institute of Tunis, photo by Henri Roussel- Roland Huet - Personal collection (left side). Macfarlane Burnet, photo by William Dargie 1960-1961, The National Portrait Gallery (right side).



Figure 13. i) Richard Edwin Schope (1901-1966), courtesy of the Rockefeller Archive Centre, ii) Patrick Playfair Laidlaw (1881-1940), iii) George Keble Hirst (1909-1994), portraits (from left to right).

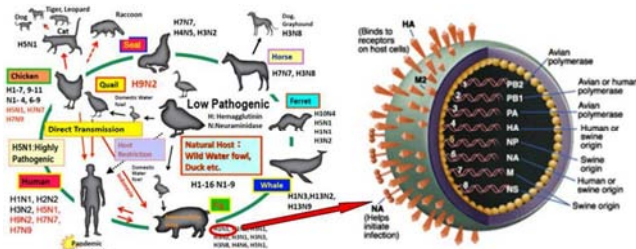


Figure 14. The avian and mammalian viruses strains through mutations (right side). Triple-reassortant swine influenza, Influenza A - subtype H1N1 virus strain, reconstructed after an electronic microscope depiction.

3. Hypotheses About the Point Break of the Virus

Various hypotheses of the epidemic's starting point emerged soon after the first wave. Some hypothesized that flu originated in East Asia. French Claude Hannoun, the leading expert of the 1918 pandemic for the “*Institute Pasteur*”, suggested that the first strain of the virus was likely to have come from China, mutating in America somewhere near Boston before spreading to France, with the movement of troops, causing the pandemic. Other hypotheses such as Spain, Kansas, and Brest are also mentioned by researchers [28].

4. Epilogue

The Spanish influenza virus was a progenitor of the modern influenza A - subtype H1N1 virus, and accomplished to be spread throughout the world, killing more than the First world War. As a zoonosis, Influenza A viruses are notorious for their continuous in-field genetic interplay among avian species, swine, and humans, leading to an endless variety of new virus strains and the unpredictable onset of new pandemics. By tracing the origins of such deadly viruses, we may alert ourselves towards such threats. History could teach us both how a virus could cause a pandemic, and what measures we could plan and energize to confront local and global outbreaks. Since the discovery of the exact cause of the influenza A, that is the demonstration of its viral nature, and the description of the characteristic properties of the virus, scientists and physicians struggle to discover effective means of prevention through vaccination against a virus eternally mutating [Figure 14].

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