Will History Repeat Itself? The Spanish Influenza: Its Past, Present, and Future

Author: Paul Ginelli

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Will History Repeat Itself?
The Spanish Influenza: Its Past, Present, and Future

Paul Ginelli

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Dr. Kathleen Dunn, Advisor

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Abstract

Nearly a century ago, a deadly pandemic swept the globe, taking with it over 25 million lives. This pandemic was caused by the elusive Spanish influenza of 1918. Although many decades have passed since this pandemic, research has yet to uncover the exact origin of the Spanish influenza and the cause of its increased virulence. By examining the current research on the Spanish influenza, some of the secrets of this virus can be uncovered. Most of today’s research supports the theory that the hemagglutinin receptor of the Spanish influenza was the most likely source of its potency and that it was an amalgamation of swine and human strains created from a common avian strain that created this virus. Based upon the information that has been uncovered, there is a considerable chance that the Spanish influenza or a similar strain could return in the future. The processes of recombination and reassortment create an endless amount of genetic variants of the virus and any one of them has the potential to be lethal. Although a natural emergence of lethal influenza is a potential threat, the artificial reconstruction of the Spanish influenza or another lethal strain for the purposes of bioterrorism may be an even bigger threat. Thus, it is necessary for researchers to press on with their search for the secrets of the Spanish influenza so that a future outbreak can be avoided. As researchers continue to do their job, the government must also take action and develop the most efficient approach to protecting the public from deadly strains of influenza.
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1. **Introduction**

Over 80 years ago, a horrifying pandemic swept the globe, taking with it over 25 million lives. This unstoppable force was the Spanish influenza of 1918. Although it has been decades since the Spanish influenza struck the world, there are still very few answers as to why this strain of influenza was so deadly. Even after nearly a century of research, scientists have not yet determined with certainty the origin of the Spanish influenza, nor have they settled upon the cause of its increased virulence. Although the Spanish influenza occurred long ago and is forgotten by many, the fact that today’s researchers believe a pandemic of similar proportions could arise reveals that the Spanish influenza still deserves our attention today.

In order to solve the mystery of the Spanish influenza and create a plan of attack against future outbreaks, it has been necessary to conduct an intensive examination of this lethal viral strain. Currently, there are several prevailing views on how the Spanish influenza arose and why it is was so potent. Although each theory claims a different origin of the viral strain, they all agree that the lethality of the Spanish influenza is most likely due to a variation in the virus’ hemagglutinin receptor allowing the virus to infect more efficiently.

This paper will attempt to show that an altered form of the hemagglutinin surface protein is the most conceivable cause of the Spanish influenza’s virulence. This paper will also establish that the mutated attachment site was created by an amalgamation of swine and human strains of the influenza virus that were both created from an ancestral avian strain. By examining the current research and revealing the most probable
explanation of the Spanish influenza, some of the secrets of this deadly virus may be uncovered so that a similar pandemic can be avoided in the future.
2. **A Brief History of the Pandemic**

Before discussing the Spanish influenza from a molecular standpoint, it is important to examine the history of the pandemic that this deadly viral strain brought upon the world. The Spanish influenza struck the world in two massive waves. The first wave began in the spring of 1918 in the United States and proceeded to spread across the globe. This first wave was much weaker than the following wave, but still considerably more virulent than any other influenza epidemic the world had ever seen. Just as this initial wave was beginning to wane, a second, more lethal wave began to sweep the world. This second sweep would prove to be the most devastating strain of influenza the world has ever known.

It was in March of 1918, that the first sweep of the Spanish influenza arose in the United States. For a number of reasons this initial outbreak of the flu was not given significant attention. The first wave of the Spanish influenza was more potent than the usual occurrences, but still not significant enough to warrant the public’s concern. One reason for the lack of concern shown for the first wave of Spanish influenza is the fact that influenza outbreaks occur every year, and thus are considered commonplace by the population (Wagner, 1999, p. 289). The appearance of the first wave during wartime was also a cause for the lack of attention. During the spring of 1918, the war was still going strong and little time or energy was available to notice this potent strain of influenza (Crosby, 1989, p. 18).

The lack of concern for the first outbreak of Spanish influenza is unfortunate because it was most likely during this period that the virus further mutated into an even deadlier form. Based on the similarity in symptoms and age of victims, scientists believe
that the first wave of the epidemic was in fact a less severe form of the Spanish influenza that struck in the second wave. The strain that caused the first wave was more virulent than ordinary strains of influenza and had an increased propensity for causing pneumonia and death, especially in victims in the prime of life. The strain in the first wave of the pandemic also had the characteristic symptom of large amounts of fluid buildup in the lungs, the same symptom seen in the second wave of the Spanish influenza (Crosby, 1989, p. 20-21). The extensive similarities between the strains in the first and second waves of the epidemic are evidence that it was the same basic strain that caused both the first and second waves of the Spanish influenza strain.

After surfacing in the United States, it is thought that the first wave of Spanish influenza made its way into Europe on ships carrying American troops across the Atlantic. The first appearance of the Spanish influenza in Europe was in an American camp close to Bordeaux. This camp was a main point of arrival for troops coming from the United States (Crosby, 1989, p. 25). Based on this point, it would appear that American troops were the source of the Spanish influenza in Europe. Once in Europe, the Spanish influenza was influenced by the frequent mobilizations and censorship associated with wartime and rapidly spread throughout Europe and Asia (Crosby, 1989, p. 28). Within four months of its initial outbreak in the United States, the first wave of the Spanish influenza had spread across the entire world (Crosby, 1989, p. 28).

Although the initial outbreak of the Spanish influenza was not extremely lethal and was ignored for the most part, it is possible that this first wave gave the virus the opportunity to acclimate itself to the new human host and replicate enough to have massive amounts of virus available for the second wave of infection. The second wave of
Spanish influenza appeared in September of 1918, at Camp Devens in Massachusetts (Crosby, 1989, p. 4). This wave was initially diagnosed as cerebrospinal meningitis because “the abruptness of the onset of the disease and the degree to which it overwhelmed the patient … seemed far too extreme to be attributed to influenza of any kind” (Crosby, 1989, p. 5). Doctors believed that the soldiers’ symptoms, including headache, fever, weakness, and the sudden onset, pointed towards meningitis. Further examination of patients, however, revealed that other symptoms such as coughing, sore throat, running nose, and aching backs and legs were also present. These symptoms were more similar to those attributed to influenza than to those of meningitis. “The lethality of the Spanish influenza was in part due to its causing hemorrhaging and extensive cell damage in pulmonary tissue … Victims essentially drowned in their own body fluids” (Wagner, 1999, p. 413). As more and more troops showed up with what was being called cerebrospinal meningitis, doctors began to reconsider their initial diagnosis. Some of the soldiers’ symptoms were those of meningitis, but the prevailing symptoms indicated an infection in the upper respiratory tract (Crosby, 1989, p. 5). After observing all of the influenza symptoms and the pulmonary damage inflicted upon the victims, medical examiners were compelled to change their diagnosis from meningitis to severe influenza.

Soon after the initial appearance of this new virulent form of Spanish influenza at Camp Devens, outbreaks of this deadly flu arose all over the United States. Across the nation, people were taking ill and dying within 48 hours of the onset of their symptoms. This strain of influenza differed from previous strains in that it had an elevated propensity for causing fatal pneumonia and did so much more rapidly (Crosby, 1989, p. 5). The Spanish influenza strain was also much more fatal to individuals in the prime of life, as
opposed to just the young and old as previous strains of influenza had been (Crosby, 1989, p. 21). Unlike the first wave, the lethality of this second wave of Spanish influenza caught the attention of the world. However, the war was still going on and money, doctors, and nurses were scarce. It was difficult to mount a unified attack on the pandemic and it was therefore able to spread just as effectively as the first wave (Crosby, 1989, p. 49). Perhaps if the Spanish influenza had appeared during peacetime, there would have been enough resources available to concentrate on containing the epidemic and ending it much more quickly. Unfortunately, countries were so consumed with the war that it was impossible to focus on the immense task of eradicating an epidemic.

**Figure 1. Death rates in the United States.**

In the Spring of 1919, one year after the first wave showed itself in the United States, the second wave had disappeared and the Spanish influenza pandemic was over. There was a brief resurgence of a strong influenza strain in the winter of 1920, but it quickly disappeared and was not considered to be the Spanish influenza strain (Crosby, 1989, p. 203). All told, the Spanish influenza pandemic claimed over 25 million lives, including over 600,000 in the United States (Wagner, 1999, p. 413). The cause of this
tremendous loss of lives deserves to be fully understood and will be thoroughly analyzed in the next section.
3. Shadowy Origins of the Virus

In order to learn more about the cause of the Spanish influenza’s potency, it is first necessary to show the origin of the lethal strain. If the origin of the deadly strain can be pinpointed, there may be some light shed upon the reason for its increased virulence. To better understand how the influenza virus became so virulent, general features of this virus will be discussed. Basic details of the influenza virus, including its structure and life cycle, are consistent with current theories about the origin of the Spanish influenza strain. It will be shown that evidence points to an amalgamation of swine and human strains that resulted in an altered hemagglutinin surface protein. Although there may be other possible alterations in the Spanish influenza strain that contributed to its virulence, the pivotal role that hemagglutinin plays in viral infection suggests that this protein is a likely source of the 1918 strain’s lethality.

The structure and life cycle of the influenza virus reveal influenza’s potential for creating a plethora of genetic variants that could possibly be deadly. For complete information about the influenza structure and life cycle, refer to Basic Virology, by Wagner and Hewlett. The influenza virus is an enveloped, negative-sense RNA virus with a multipartite genome. Although there are three types of influenza viruses, including types A, B, and C, type A is the cause of recurring outbreaks around the world. Type A influenza has eight separate parts to its genome that are all packaged in a single virion. The segmented genome of the influenza virus is one of the factors that allows for the possibility of creating lethal strains of the virus during the viral life cycle.
In the life cycle of the influenza virus, the machinery of a host cell is taken over and used to create multiple copies of the virus. For influenza, the process of replication begins with attachment of the viral membrane glycoproteins, such as hemagglutinin and neuraminidase, to the host cell’s receptors. The enveloped virus is then taken into the cell by a vesicle in the process of endocytosis. Once inside the host cell, the viral envelope fuses with the vesicle and releases the eight segments of its genome. These segments are in the form of ribonucleoproteins (RNPs), negative-sense RNA strands surrounded by proteins. These eight RNPs enter the host cell’s nucleus, where they are transcribed into positive-sense mRNA strands using the viral enzyme transcriptase. In order to synthesize viral mRNA, the virus must first steal the 5’ caps of the host cell’s mRNA. By stealing the caps of the host cell’s mRNA, the influenza virus hinders host
translation, but allows for viral translation to take place. The viral proteins are then translated and the components of the new virions move to the host cell’s membrane, where RNA replication and virion assembly begins.

It is during the packaging process that the possibility for new strains to emerge can be seen. The incorporation of the eight segments of the viral genome into each new virion is not strictly regulated by the influenza virus. Although much is unknown about this process, it is likely that during RNA packaging the influenza virus may ensure that all the necessary components of the genome are included in new virions, but it does not regulate where these components come from. Thus, when a host cell is simultaneously infected by different strains of influenza, it is possible that genomic segments from these different strains will be incorporated into each virion.

The common occurrence of recombination events during genome replication also contributes to variations in the virus (Ahlquist, 2002). Influenza uses RNA-dependent RNA polymerases (RdRps) to replicate and transcribe its RNA genome (Ahlquist, 2002). The role of these RdRps is to operate in complexes that bring the polymerase to RNA templates and organize the steps of RNA synthesis (Ahlquist, 2002). The RdRps, however, have high error rates and allow for template switching during RNA copying (Ahlquist, 2002). Strand switching allows the virus to acquire portions of genes from other viruses that may be involved in a mixed infection (Ahlquist, 2002). If multiple viruses are copying their RNA genomes prior to packaging, and the error-prone RdRps exchange RNA templates with other viruses, the result is a recombination event that often creates new viral strains. Although recombination does not always produce viral strains
that exhibit increased virulence. “Genome comparisons imply that such RNA recombination has been the major force in RNA virus evolution” (Ahlquist, 2002).

It can now be seen that when genetic material from different strains is mixed together in a single virion due to packaging mistakes or template switching, the result is a new strain that may have different attachment proteins with a heightened affinity for human cells. It should not be assumed that every case of mixed infection will result in a deadlier form of influenza. It is important, however, to realize that when a vast source of genetic material is available for a virus to utilize, there is an increased chance of creating a more potent strain, such as the Spanish influenza.

Figure 3. Life cycle of influenza virus.
Type A influenza is able to infect a variety of different hosts, which can result in various combinations of infections between swine, avian, and human strains. This scenario of mixed infection is what researchers currently believe contributed to the creation of the deadly Spanish influenza strain. Research now suggests that the Spanish influenza was created from a rare merger of swine and human strains, both descending from an ancestral avian strain, that resulted in a new hemagglutinin membrane protein with the ability to infect more efficiently. Although this theory is not completely worked out, it has not been disproved by conflicting data and still remains the most likely scenario for the creation of the Spanish influenza.

In “1918 Spanish influenza: The secrets remain elusive”, Robert Webster provides support for the theory that the Spanish influenza was created from swine and human strains of influenza originating from an avian strain (Webster, 1999). Webster relies upon data obtained from tissue samples of victims of the 1918 pandemic. After the pandemic in 1918, these samples were taken from victims and preserved in paraffin for future research or found later on in victims buried in permafrost. Webster explains that the current method of studying these samples is to use reverse transcriptase-PCR technology to amplify the samples and obtain the sequences of the virus’s genes. After analyzing such sequences, certain conclusions were reached (Webster, 1999).

Webster believes that the Spanish influenza strain resulted from an exchange of genetic material between swine and human strains during a mixed infection. Although the mixing of genomic material between different strains occurs randomly during virion packaging and thus does not always yield more virulent strains, Webster feels that one such event was able to create the deadly Spanish influenza strain. The data also show
that the Spanish influenza strain did not involve an avian strain during this mixed infection, but may have been related to an avian ancestor. The sequence of the hemagglutinin gene revealed that the Spanish influenza virus did not create any of the polybasic amino acids that are characteristic of the hemagglutinin of extremely virulent avian influenza strains (Webster, 1999). This piece of data indicates that an avian strain could not have contributed genetic material during the mixed infection that created the Spanish influenza. Sequencing of the Spanish influenza’s hemagglutinin gene also revealed that this lethal strain was similar to swine strains. So far, these analyses support the theory that the 1918 strain arose from a mixed infection involving pigs, but not birds. Although the mixed infection did not involve avian strains, there is evidence that the source of the swine and human strains was a bird. By creating phylogenetic trees, it can be seen that the Spanish influenza’s hemagglutinin is closely tied to swine and human strains, but the antigenic and receptor binding sites of the virus display a trace amount of avian qualities (Webster, 1999). These avian characteristics were not substantial enough to alter the tropism of the virus, but they do reveal ancestral ties. This evidence supports the notion that human and swine strains of influenza originated from an avian ancestor and later exchanged genomic segments during a mixed infection to create the Spanish influenza.

Webster’s paper, “1918 Spanish influenza: The secrets remain elusive”, also sheds some light on the time and location that the Spanish influenza first arose. By studying epidemiologic data, it can be seen that there was a deadly influenza epidemic in the pig population of the United States that coincided with the human epidemic. Although existing records do not provide much evidence, they do suggest that a virulent
strain of influenza existed in the pig population prior to the initial appearance of the Spanish influenza in humans during the spring of 1918 (Webster, 1999). This may suggest that the Spanish influenza was first created in the pig population and eventually made its way into the human population. This jump from pigs to humans may have occurred in a Midwest farm, where pigs and farmers are often in close contact with each other. After this mixed infection was established in the human population, a deadlier form of the virus was created during a chance virion packaging event. This notion is backed up by the fact that the influenza virus has the tendency to mutate rapidly when it enters a new host (Webster, 1999). Also, it has been determined that the region of the influenza genome that evolves the most when the virus enters a new host is the section coding for hemagglutinin (Webster, 1999). The higher rate of evolution for the hemagglutinin protein is based upon analysis of the genomes of other highly virulent strains that have entered new hosts (Webster, 1999). The reason for this higher rate of evolution is unknown, but perhaps it is due to the increased selective pressure placed upon the proteins that determine host specificity, such as hemagglutinin. Thus, if a virus mutates rapidly upon entering a new host, it is highly likely that after making the leap from the pig population to the human population, the Spanish influenza further mutated and became increasingly virulent throughout the first wave of infection. This notion provides more information about the source of the Spanish influenza and supports the idea that the strain was in some way related to pigs.

The theory of mixed infection between swine and human influenza is also supported by Gibbs et al (2001), which proposed that the hemagglutinin protein was the most likely cause of the Spanish influenza’s increased virulence. This hypothesis was
made based on data showing that influenza virulence is mostly established by hemagglutinin and that highly pathogenic strains of influenza often contain mutations in the hemagglutinin gene (Gibbs, 2001). In this study, several hemagglutinin gene sequences from humans, pigs, and birds were aligned. Then, using a computer program, every possible amalgamation of these three sequences was analyzed in order to find a combination that resembled the 1918 hemagglutinin sequence. Of all the possible recombination events, only one mixture was similar to that of the Spanish influenza. This particular combination was created using only swine and human sequences, not avian sequences (Gibbs, 2001). These results suggest that the Spanish influenza was created from human and swine strains, but not with avian strains.

Further analysis of the recombined sequence identified the specific sequences of the Spanish influenza’s hemagglutinin gene that were of swine and human origin. It was found that the “globular domain” of the Spanish influenza’s hemagglutinin that contains antigenic and host cell receptor binding sites was created from proteins encoded by a swine influenza strain. The “stalk” section of the hemagglutinin protein that secures the hemagglutinin to the virus’s envelope was created from proteins encoded by a human influenza strain (Gibbs, 2001). As previously discussed, the recombination event that created this new hemagglutinin protein is characteristic of RNA viruses (Ahlquist, 2002). Due to the template switching allowed by error-prone RdRps, recombination events are a common occurrence between the RNA of different viruses during a mixed infection (Ahlquist, 2002). Thus, it can be seen that a common recombination event during genome replication could have led to the creation of a hemagglutinin protein consisting of genetic material from swine and human influenza strains.
Figure 4. Front, top, and side views of the hemagglutinin protein.

The notion that the human and swine strains of influenza arose from a common avian ancestor was also confirmed by Gibbs et al (2001). By studying evolutionary ties, it was shown that an avian strain of influenza found its way into mammals and then split into a human and a swine lineage. It is thought that this jump from birds to mammals occurred after 1900, but before the pandemic of 1918 (Gibbs et al, 2001). After the two lineages were established, a recombination event between the swine and human lineages took place during a mixed infection. It is believed that this incident resulted in a new form of influenza with a heightened virulence. Data from the phylogenetic trees shows that this new strain of influenza arose directly before the outbreak in 1918, and is most likely the Spanish influenza strain (Gibbs, 2001). These results are summarized in Figure 8, which shows the ancestry of the Spanish influenza. The triangle indicates the jump from birds to mammals, and the circles represent recombination events between the connected lineages. The bars symbolize the hemagglutinin gene and its composition (Gibbs et al, 2001).
Earlier studies of Taubenberger et al (1997) also provide evidence that the Spanish influenza arose from swine and human strains having an avian ancestor.

Samples of the Spanish influenza virus were obtained from The Armed Forces Institute of Pathology in Washington, D.C., where tissue from American soldiers who died from the Spanish influenza is preserved. Seven soldiers were selected who died within one week of their symptoms appearing so that there would have been enough time for the virus to replicate and produce a reliable sample (Taubenberger, 1997). After acquiring the preserved samples of the Spanish influenza virus, reverse transcriptase-PCR was used to amplify the genes encoding hemagglutinin, nucleoprotein, neuraminidase, and matrix proteins 1 and 2, and a sequence analysis was used to create a phylogenetic tree.
In this tree, the Spanish influenza gene sequences obtained from the American soldiers were compared to 30 other sequences from various present-day mammal and avian strains. The results from this analysis showed that the sequences obtained from the Spanish influenza were closely related to mammalian strains, especially humans and pigs, but not to any bird strains (Taubenberger, 1997). The data also revealed that the hemagglutinin gene was most likely the cause of the Spanish influenza’s increased virulence because it was more closely related to the swine and human strains than were the other 1918 viral genes. Therefore, the hemagglutinin protein was altered more than the other Spanish influenza proteins (Taubenberger, 1997).

To further demonstrate that the Spanish influenza did not arise from a recombination event involving birds, the sequences of the hemagglutinin genes from the Spanish influenza were examined to determine if they contained certain avian sequences (Taubenberger, 1997). Avian strains of influenza with a heightened virulence typically contain a sequence in their genome that codes for a series of basic amino acids on a hemagglutinin cleavage site (Taubenberger, 1997). It was also known that this sequence encoding the basic amino acids had not been found in any mammalian strains (Taubenberger, 1997). Thus, determining whether or not the Spanish influenza strain contains such a sequence would provide more information about its origin. To determine if the Spanish influenza strain contained this avian sequence, Taubenberger created primers that flanked this specific avian sequence and attempted to amplify the sequence using the Spanish influenza strain in a PCR reaction. There was no evidence to demonstrate that the Spanish influenza hemagglutinin gene contained this sequence. This result further indicated that avian influenza strains most likely did not take part in the
recombination event that created the Spanish influenza (Taubenberger, 1997) and thus supported the subsequent sequence analysis by Gibbs et al (2001). While an avian strain was not involved in the primary reassortment, the Taubenberger group provided phylogenetic evidence suggesting that the Spanish influenza had an avian ancestor. Further analysis suggested that the avian ancestor jumped into a mammalian host before the 1918 pandemic (Taubenberger, 1997).

The vast amount of evidence provided by the current research on Spanish influenza all points to a specific mechanism for the creation of this deadly strain. The studies show that at some point in the early 1900’s, an avian strain found its way into an unknown mammalian host. Once inside this mammalian host, the avian strain evolved into a human lineage and a swine lineage. Then, during a mixed infection, these swine and human strains exchanged genetic material. This genetic exchange is thought to have been caused by either the mixing of genomic segments during packaging, or the recombination of genomic RNA due to mistakes made by the RdRps. The result of this genetic exchange was a new form of the influenza’s hemagglutinin protein, consisting of parts from both swine and human strains. Although other proteins may have been altered as well, researchers agree that the hemagglutinin protein is the most likely cause of the Spanish influenza’s increased virulence. The reasons why this new hemagglutinin made the Spanish influenza so deadly will be discussed in the next section.
4. **Why was the Spanish influenza so Deadly?**

The exact reasons as to why this new strain of influenza had the ability to cause so much damage to victims, especially to young adults in the prime of their lives, have yet to be uncovered. After studying most of the viral genome, the mechanism for this pathogenesis is unknown, but there are several proposals as to why the altered hemagglutinin protein may have given the Spanish influenza strain such virulence.

The hemagglutinin protein is responsible for allowing the influenza virus to enter its host cell. When the influenza virus comes in contact with a potential host cell, the hemagglutinin protein attaches to the sialic acid receptor of the host cell membrane to anchor the influenza virus and initiate the endocytosis process. Research has shown that the ability of influenza A viruses to infect depends primarily on the hemagglutinin protein (Gibbs, 2001). Thus, it is clear that a change in the hemagglutinin protein could potentially strengthen the virus’s ability to anchor itself to the host cell and cause an infection. In fact, it has been found that if the hemagglutinin gene is mutated, extremely virulent strains of influenza can be generated (Gibbs, 2001).

![Figure 6. Influenza’s hemagglutinin protein.](image-url)
Research done by Gibbs suggests that the hemagglutinin gene of the Spanish influenza strain was in fact altered during a mixed infection involving human and swine strains. This mutated gene encoded for a hemagglutinin protein with a swine influenza “globular domain” and a human influenza “stalk” (Gibbs, 2001). This new hemagglutinin may also have been able to bind more efficiently to the host cell’s sialic acid receptor or have changed its target host cells altogether, perhaps to cells in the lungs where it could cause pneumonia more easily (Gibbs, 2001). Any one of these scenarios could possibly result in a more virulent influenza strain.

Since there is no complete explanation for why the altered hemagglutinin protein made the Spanish influenza so deadly, it is difficult to determine why it also had the unusual ability of infecting young adults in the prime of their lives. There is one possible theory offered by Sir MacFarlane Burnet, the 1960 recipient of the Nobel Prize for Medicine. Burnet suggests that the increased virulence of the Spanish influenza induced a more powerful response from the human immune system. The immune system could not mount a specific attack on the newly encountered form of the virus, so it released a generalized response in the form of intense inflammation in the area of infection. This powerful inflammation in the pulmonary tract caused a large amount of fluid buildup in the lungs, which resulted in death for the infected individual. Young children and older adults have a weaker immune system than that of a young adult, so the inflammation in the young and old was not strong enough to fill their lungs with fluids and drown them (Crosby, 1989, p. 221). Although this theory was developed before the composition of the Spanish influenza’s hemagglutinin was discovered, it still remains possible. Perhaps if the altered hemagglutinin was able to bind more efficiently to host cells, then the virus
would be able to multiply more efficiently, resulting in unusually large amounts of virus in the body. This massive amount of foreign matter would evoke an intense response from the immune system that could potentially flood the lungs. This is a conceivable explanation for the Spanish influenza’s unique ability to kill more young adults than an ordinary strain of influenza.

Unfortunately, no studies have yet been conducted to prove any theory regarding the Spanish influenza’s virulence. In order for the pathogenesis of the Spanish influenza to be determined, experiments must be conducted using reconstructed portions of the 1918 virus. Current techniques will soon allow researchers to recreate the 1918 strain and determine the exact mechanism of pathogenesis.
5. **Future Research**

Studies to date have suggested that an altered form of the hemagglutinin protein may be the main reason for the 1918 influenza’s virulence. Research has focused on the hemagglutinin protein because it has traditionally been linked to the increased virulence associated with flu epidemics. However, there is still much more work to be done in order to determine the exact origins of the Spanish influenza and the reasons for its potency. The sequence of the entire Spanish influenza genome has yet to be completed and investigators are still examining characteristics of the ancestor strains. Researchers believe that when these areas of study have been exhausted, the mystery of the Spanish influenza will finally be solved.

Once the entire genome of the Spanish influenza is found and sequenced, the exact cause of its potency may be determined. One particular sequence of interest is the gene encoding viral polymerase. When viral polymerase is altered due to a mutation, the target host and area of infection are often changed (Zucker, 2002). Influenza utilizes three polymerases including PA, PB1, and PB2, during the course of infection. These polymerases are associated with the RNPs of the virus throughout the infection cycle. Thus, one possible effect of an altered polymerase would be to change the RNP’s ability to move past the nuclear envelope of the host cell. Perhaps an altered polymerase would allow improved entry into the nucleus of a new target cell, and thus the virus would attack a different region of the respiratory tract. PB1 and PB2 are also responsible for the process of cap stealing, which allows for viral RNA production. If either of these polymerases were altered, the virus could possibly improve its ability to replicate in the host cell. It can be seen that a change in a polymerase could potentially cause the virus to
target more areas in the lungs or improve its replication ability, resulting in a larger immune response and greater fluid buildup. Learning more about the polymerase of the Spanish influenza may also reveal that the heightened virulence of this strain was due to the combined effects of altered hemagglutinin and polymerase.

Obtaining the complete sequence of the Spanish influenza genome may also allow medical researchers to determine how to protect the population from another such outbreak. With the full 1918 genome available to them, researchers will be able to develop vaccines and anti-viral drugs to prevent another outbreak in the event that the Spanish influenza or a similar strain were to strike again. The effectiveness of existing drugs could also be tested if the complete sequence of the Spanish influenza genome was known (Webster, 1999).

It is also important to learn more about the precise origin of the Spanish influenza strain so that its heightened virulence can be fully understood. Although current research has determined that the Spanish influenza was most likely created from swine and human strains stemming from an avian ancestor, samples of these strains have still not been found. Researchers also hope to find the weaker strain of the virus that caused the first wave of the Spanish influenza. Researchers believe that samples of these elusive strains will most likely turn up in avian feces and mammalian tissues that have been preserved in permafrost since the 1918 outbreak (Webster, 1999). In fact, explorations into the permafrost of the Antarctic to find the frozen feces of gulls and penguins in past nesting locations have already begun (Webster, 2001).
6. *Could the Virus Return?*

Although the Spanish influenza has been unseen for over 80 years, many of today’s researchers feel that another deadly strain of influenza may resurface in the future. Although random, the processes of reassortment and recombination can take advantage of the vast amount of genetic material available during mixed infections to create an endless number of new influenza strains. In fact, such occurrences have already created deadly influenza strains in 1957, 1968, and 1997. An even more threatening possibility is the intentional reconstruction of the 1918 influenza virus in the laboratory. Thus, it is important to examine all possible sources of the Spanish influenza or similar strains so that they can be avoided in the future.

The occurrence of another reassortment or recombination that leads to a virulent strain is one possible source of another deadly strain of influenza. Recombination and reassortment are common events that create an infinite amount of new genetic combinations. Although not every new influenza strain that is created will have heightened virulence, the number of possibilities is so great that virulent strains can be created regularly. In fact, more deadly strains of influenza have already surfaced due to such random events. The 1957 Asian flu and the 1968 Hong Kong flu were both the result of reassortment during mixed infection (Webster, 2001). These influenza strains both had genomes consisting of components from avian and human strains (Webster, 2001). In 1997, another deadly influenza virus emerged in Hong Kong (Webster, 2001). This virus was found to have altered polymerase and hemagglutinin proteins possibly caused by recombination (Webster, 2001). Thus, recombination and reassortment events remain potential sources for highly virulent influenza.
In a time when acts of bioterrorism are constantly appearing across the globe, the intentional reconstruction of the Spanish influenza by terrorist groups is perhaps the most threatening source of this deadly virus. Research conducted on the Spanish influenza has already yielded the sequence of a large portion of the 1918 genome, and these data can easily be acquired on the Internet. Soon the entire genome of the 1918 virus will be uncovered, and with this sequence in hand, a terrorist group could potentially reconstruct this deadly virus and use it as a weapon. Using existing plasmid-based reverse genetics techniques, it is currently possible to artificially create strains of influenza, such as the Spanish influenza, that have heightened virulence in specific hosts (Webster, 2001). In fact, Terrence Tumpey and his research team have already created influenza strains containing the 1918 hemagglutinin, neuraminidase, and matrix proteins (Tumpey, 2002). Although these strains were created under biosafety level 3 conditions for research purposes only, the fact that the Spanish influenza has already begun to reemerge is quite frightening. Due to the power of current genetic technology, it is extremely important for researchers to make careful decisions when experimenting with highly virulent strains of influenza and for the government to closely monitor any such activities.
7. **Precautionary Measures**

Now that the potential threat of the Spanish influenza or similar strains has been demonstrated, it is clear that precautionary measures must be taken to prevent future pandemics. Fortunately, groups such as the World Health Organization (WHO), National Respiratory and Enteric Virus Surveillance System (NREVSS), Food and Drug Administration’s Vaccine and Related Biological Products Advisory Committee, and Centers for Disease Control and Prevention (CDC) are constantly monitoring the influenza strains around the globe and have developed protocols in the event of a future outbreak. These organizations have done an excellent job in protecting the public from the influenza virus, but the time period required to identify, study, and develop a vaccine for a new strain of influenza is still too long. In order to strengthen the fight against influenza, a global lab must be created to reduce the time needed to protect the public from emerging strains. The development of new vaccines and drugs is also necessary to prepare for new strains of influenza.

Current organizations monitoring the influenza virus have done much to protect the public from influenza, but their efforts would be greatly improved by a global lab. Each year, WHO uses its worldwide facilities to collect and study nearly 200,000 viral samples from almost a billion different influenza cases (Layne, 2001). After studying these samples, WHO holds formal meetings to determine which strains pose the biggest threat to public health. At this point, manufactures have approximately 6 months to develop and produce a vaccine that will be given to nearly 200 million patients worldwide in the next 3 months (Layne, 2001). This process has been used for many years and has done an excellent job protecting the public. There are, however, some
drawbacks to the current course of action. One problem is that the methods used to study
the influenza samples take a great deal of time and effort to conduct. Therefore, not all of
the influenza samples are completely characterized (Layne, 2001). Even if a strain is
fully analyzed, the entire process from collecting the sample to understanding the virus
takes anywhere from a few weeks to a few months (Layne, 2001). During this time, a
virulent strain could easily spread throughout the population.

The Institute of Medicine and National Academy of Engineering feel that the
solution to the problems with current detection methods is the formation of a global lab.
This centralized lab would utilize highly advanced biological, informatics, and
engineering technology to quickly analyze influenza samples collected and sent in by
WHO (Layne, 2001). Using automated systems, the global lab would be able to fully
analyze a sample within days of receiving it. Data on analyzed strains would be placed
on the Internet for organizations across the globe to utilize (Layne, 2001). It would take
this global lab only a few years to produce a $10^{15}$ bit-sized database of all known
influenza data that would be enormously helpful in fighting the virus (Layne, 2001). The
global lab would also be able to monitor influenza strains circulating in populations of
animals with a history of passing influenza strains into the human population (Layne,
2001). Analysts believe that a global lab could be up and running at full capacity within
5 years as soon as the $45$ million price tag is covered (Layne, 2001). Although the cost
is high, the government could easily afford it and would instantly save millions of dollars
in influenza studies and vaccine development as soon as the global lab was complete.
Cost aside, the global lab would also save thousands of lives and protect the public from
any dangerous strains of influenza that may surface.
Of course, a global lab or any other organization would be useless if there were no vaccines or drugs for them to fight an influenza outbreak with. Thus, it is important to create and stockpile effective drugs before another pandemic occurs. Currently, vaccines are the prevailing method of attack against the influenza virus (Zucker, 2002). These vaccines consist of inactive hemagglutinin and neuraminidase subunits retrieved from different strains of the influenza virus (Laver, 2001). Unfortunately, the effectiveness of vaccines is limited by the accelerated mutation rate of influenza (Zucker, 2002). Using new reverse genetics techniques, researchers will soon be able to create vaccines much easier than before. Researchers can now genetically engineer attenuated vaccines with any combination of desired components and abilities. These new procedures will allow a vaccine for a new strain of influenza to be created in only a few months, as opposed to the six months it takes now (Webster, 2001). During these months, however, a new strain of influenza could rapidly spread throughout the population.

In order to protect the public during the time it takes to prepare a new vaccine, it is necessary to use antiviral drugs (Webster, 2001). The antiviral drugs that exist today include neuraminidase inhibitors and M2 ion-channel inhibitors. Neuraminidase inhibitors act by preventing the surface protein neuraminidase of the influenza virus from cleaving the sialic receptors on the host cell. This action prevents the new virions from detaching from the host cell and spreading the infection (Tumpey, 2002). Examples of neuraminidase inhibitors currently available include zanamivir, which is inhaled, and oseltamivir, which is taken orally (Zucker, 2002). Another form of attack is the M2 ion-channel inhibitors, which prevent uncoating and the release of the RNPs from the
endosome. The result of this stoppage is the prevention of viral entry into the host cell cytoplasm (Tumpey, 2002).

In an interesting experiment, one group of researchers tested the effectiveness of current antiviral drugs on strains containing components reconstructed from the 1918 viral genome. Using the current knowledge of the Spanish influenza’s genome, this group created influenza strains containing the same hemagglutinin, neuraminidase, and matrix proteins that the original virus had in 1918. It was found that strains containing both the 1918 hemagglutinin and neuraminidase proteins were extremely virulent and lethal in mice (Tumpey, 2002). The potency of the 1918 strains was further demonstrated when control strains containing the hemagglutinin and neuraminidase proteins from current human samples were not able to kill the injected mice (Tumpey, 2002). It was also found that existing antiviral drugs were able to prevent the strains containing Spanish influenza components from infecting tissue cultures and mice. Both the neuraminidase inhibitors and the M2 ion-channel inhibitors were proven effective against the recombinant virus created in this experiment (Tumpey, 2002). The results from this experiment are very encouraging and suggest that if the Spanish influenza ever returned, current drugs would effectively stop it.

It seems as though antiviral drugs would be the most effective method of preventing another influenza pandemic like that of 1918. Antivirals have been proven to stop influenza from replicating, but they are only effective if used early on in the infection. These drugs cannot reverse any damage that the virus has already caused, so it is necessary to use them as soon as the infection begins (Laver, 2001). In order to detect an influenza infection early on, it is necessary to create diagnostic tests that will reveal if
a patient’s symptoms are being caused by influenza (Laver, 2001). Now that researchers have determined existing drugs can be used to combat influenza pandemics, it is up to the government to stockpile these antivirals. These drugs will only be effective if they are available in large amounts and a plan for their immediate distribution in the event of an outbreak is developed. Unfortunately, there has been little effort shown by the government in stockpiling such drugs, and drug companies are not producing antivirals because it is not cost effective (Laver, 2001). The possibility of another deadly influenza strain emerging from nature is too significant to be ignored. The intentional creation of lethal influenza is also a cause for concern. The government has taken many measures to avoid terrorist attacks and has recently funded a national smallpox vaccination to thwart any acts of bioterrorism employing smallpox. Therefore, there is no reason why the government should ignore the very real threat of terrorists utilizing lethal influenza to attack the public.
8. Conclusion

Now, after analyzing the past, present, and future of the Spanish influenza, it is apparent that this virus cannot be overlooked. The processes of recombination and reassortment are constantly creating an endless amount of genetically altered strains of the virus and any one of them could be the next Spanish influenza. Along with the threat from nature is the threat of artificial reconstruction of the Spanish influenza or another lethal strain for the purposes of bioterrorism. It cannot be stressed enough that the Spanish influenza and equally deadly strains of the virus must not be ignored. For this reason, it is important for researchers to continue their search for the elusive secrets of the Spanish influenza. So far, researchers have found that the hemagglutinin receptor of the Spanish influenza was the most likely source of its potency and that it was an amalgamation of swine and human strains from a common avian strain that created this virus. With more research, it is very likely that the mystery behind the Spanish influenza will be solved in the near future. With the knowledge that is available today and the knowledge that will be acquired in the future, it is up to researchers to fully understand highly virulent influenza, and it is up to the government to implement the most efficient approach to monitoring influenza strains circulating the globe.
References


Figures obtained from:

Cover: http://www.uct.ac.za/depts/mmi/stannard/emimages.html

Figure 1: http://www.pbs.org/wgbh/amex/influenza/maps/index.html

Figure 2: Webster, R. G. (2001). A molecular whodunit. Science, 293, 1773-1775.

Figure 3: http://www.ch.ic.ac.uk/local/projects/sanderson/images/lifecyc.gif

Figure 4: Created using Rasmol protein viewer program.


Figure 6: http://web.uct.ac.za/depts/mmi/jmoodie/influen2.html