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Investigation into the Causes and Severity of the 1918 Influenza Pandemic

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Abstract
The 1918 Influenza outbreak is regarded as one of the worst pandemics in human history due to its widespread effects across the globe and its high death rate. This death rate was unusual among influenza infections as most strains do not cause the amount of death that is seen in this outbreak, with 20 million dead as a conservative estimate and 100 million by other estimations. This pandemic was not very well contained for a plethora of reasons. Two main reasons are that it came at a time when understanding viral mechanics still escaped medical professionals, and due to the ongoing war quarantine was not a measure imposed by many cities. To understand how this virus was able to so effectively wreak havoc in the human population, it must be shown how this virus was unique not just in spread, but also in its method of killing its host. These two traits must be looked at together as the virus was able to spread so quickly and this virus was able to kill not just those with a weak immune system, but in many cases those individuals who had the best immune system to fight the infection still died from the disease. The virus was able to be so effective at spreading and causing death, due to alterations to its genome which allowed both for an asymptomatic period of the infection where the PA gene was used as a less pathogenic version (PA-X) this allowed the virus to multiply to a point where it could easily overwhelm total body defense with number of viral particles. This asymptomatic period allowed the viral transmission to spread faster than people expected as the virus would be transmitted before an infected individual knew they were sick. This allowed for another unique trait of the virus to take over, the cytokine storm. This storm used the body's own defenses to weaken it and paralyze the immune system in a way that allowed for a secondary infection to easily infect the host and cause death. This happened during this pandemic as many of those who died fell to a bacterial pneumonia infection and not the virus itself. These characteristics, combined with the virus' timing allowed for it to be the worst pandemic that mankind had experienced. As the virus both exhibited novel traits, and came at a time when preventative measures were not in place and human migration was occurring due to the war.

Keywords
Influenza, Pandemic, 1918

Cover Page Footnote
Thank you to Dr. Kristen Picardo for helping me organize my thoughts in the creation of this work

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ABSTRACT

The 1918 Influenza outbreak is regarded as one of the worst pandemics in human history due to its widespread effects across the globe and its high death rate. This death rate was unusual among influenza infections as most strains do not cause the amount of death that is seen in this outbreak, with 20 million dead as a conservative estimate and 100 million by other estimations. This pandemic was not very well contained for a plethora of reasons. Understanding the major causes has been a source of academic intrigue for the last 100 years. The two main reasons hypothesized to have caused the scale of the outbreak are that it came at a time when understanding viral mechanics still escaped medical professionals, and the fact that, due to the ongoing war, quarantine was not imposed by many cities. To understand how this virus was able to so effectively wreak havoc in the human population, it must be shown how this virus was unique not just in spread, but also in its method of killing its host. These two traits must be looked at together as the virus was able to spread so quickly and to kill not just those with a weak immune system, but also, in many cases, individuals who had much stronger immune systems. The virus was able to be so effective due to alterations to its genome which allowed for an asymptomatic period of the infection where the PA gene was used as a less pathogenic version (PA-X) which allowed the virus to multiply to a point where it could easily overwhelm total body defense with number of viral particles. This asymptomatic period allowed the viral transmission to spread before an infected individual knew they were sick. This allowed for another unique trait of the virus to take over, the cytokine storm. This storm used the body's own defenses to weaken it and paralyze the immune system in a way that allowed for a secondary infection to easily infect the host and cause death. Many of those who died during this pandemic fell to a bacterial pneumonia infection and not the virus itself. These characteristics, combined with the virus's timing, allowed for it to be the worst pandemic that mankind had experienced. The virus both exhibited novel traits, and came at a time when preventative measures were not in place and human migration was occurring due to the war.

Introduction

In 1918, an influenza pandemic of incomparable proportions swept the world. It shortened global life expectancy, lead to over 20 million deaths, and infected 20% of the world's population. This outbreak was due to a combination of factors, from human migration to the specifics of the viral strain. It was caused by a specific influenza viral strain known as H1N1. The H1N1 influenza virus was different from other strains and was more deadly and communicable than what health services were able to handle at this time. The main questions surrounding this virus are how it was unique when compared to other influenza strains, and what made it kill those with the strongest immune systems (people aged 20-40). The unique biology that this virus possessed along with the global political time in which it arose gave it its ability to be so deadly.

Several points must be addressed in order to comprehend why this strain of influenza proved to be so deadly. One must be aware of what influenza is, how it infects a host, how the immune system battles such viruses, and how influenza evolves and

changes. The environment that the virus was in during its spread is also important; as explained through developmental plasticity, the environment and genotype together are what make the phenotype that is observed.

Basics of Influenza

Influenza is a virus. A virus is a type of organism different from the other Kingdoms, a taxonomic classification, as it only acts as a living thing when inside and hijacking a host. For this reason, all viruses are parasites. Influenza, in particular, is an RNA negative virus that is further broken down into 3 subtypes: A, B, and C. Influenza-A is the most common type that infects the human population, and is further classified into protein-type nomenclature. The name comes from the types of surface protein that the virus has. There are two main surface proteins on influenza: hemagglutinin (H) and neuraminidase (N). Depending on the structural shape of the H and the N, they are assigned a specific number. Strains range from H1N1 to H9N7 with many combinations in between. Influenza is transmitted by fluid transfer from person to person. Transmission occurs much more often than people believe; tiny droplets can be released in a spray when an infected person coughs or sneezes and a new host breathes them in (Billings 1997). This highly contagious virus can even be known to cause an infection when just one virion makes it to its target, lung epithelial tissue (Zwart et al. 2009). Millions of virus particles can be in just one drop of infected fluid. However, the human body has many ways to combat these complex viruses, and, using its complex defense mechanisms, is usually able to stop the virus from compromising the body's homeostasis.

Immune System

The immune system is made up of two major components: innate and adaptive immunity. The innate immune system starts fighting before the pathogen can even reach the body's inner cells. The first part of the innate immunity is also the body's largest organ—the skin. The skin provides external immunity against microbes, acting as a physical barrier as well as expelling secretions that are toxic to most microbes. Mucus membranes coat the insides and openings of the body where the skin doesn't continue protection, secreting mucus and other fluids that prevent microbes from infecting the body. When influenza-A enters the body, it must get past the perfusion system's mucus membranes as well as that of the respiration system. Mucus is crucial; if the virus gets to the respiratory system, it can easily infect the cells and start a total body infection. The body also relies on its innate immunity response. This blocks all foreign bodies indiscriminately. Different cell-mediated proteins fight inside of infected cells and make it harder for viruses to reproduce, and leukocytes fight infected cells in the blood. Leukocytes, or white blood cells, do two major things: identify foreign organisms within the body, and destroy them through phagocytosis and lytic actions of lysosomes.

However, viruses are not easily fought off. They have an ever changing surface protein make-up, so virus identification becomes very difficult for the non-specific immune response. This makes the immune system employ some very specific leukocytes and proteins to target microbes, specifically. This second line of defense is known as the adaptive immunity. The adaptive immunity initiates the humoral response which uses the body's antibodies to target a microbe's surface proteins or

receptors. It either tags a microbe to be destroyed, or blocks its receptors, rendering it unable to infect a new host. The body uses its adaptive immunity to specialize its defense during viral infections, pursuing precisely the microbe that is causing harm to the body.

Both adaptive immunity and innate immunity utilize the humoral response, as well as the cell mediated response. While the humoral response is focused on antibodies, the cell-mediated response is focused on cell to cell signaling. Unlike its counterpart, the cell-mediated response doesn't use antibodies or inner cell proteins. Instead, a type of proteins called cytokines is used to relay information between these two systems and ensure proper immune function and type of response. The cytokines signal to a special type of leucocyte called dendritic cells to come and recognize the virus and make antibodies. It also encourages cytotoxic T cells to cause apoptosis of infected cells. This signaling is especially important in adaptive immunity, as it allows the body to "remember" what antibodies best work against it. By specializing the response, it allows for the body to only expend energy to specific tasks and block viral particles in the blood stream and be more accurate in removing the threat.

The combination of cytotoxic T cells and antibodies are usually able to overcome a virus and ensure in doesn't cause total body destruction. Unfortunately, in some cases, the immune system is overcome, and the body is unable to eliminate the virus before the infection spreads too far. A virus constantly adapts and evolves to keep ahead of the immune system's detection and destruction. It changes its phenotype to avoid discovery. Meanwhile, the immune system perseveres by specializing and changing its antibodies. It is clear that the struggle between a combative host and persistent parasite leads both sides engage in an ongoing Darwinian conflict.

Virus Genome

As stated before, influenza-A is an RNA negative virus. However, although that explanation works as a classification, it does not describe the make-up of its genome. Influenza-A has a segmented genome. That means the genome is composed of eight segments that can be transcribed to create more viral RNA or viral mRNA, but the virus lacks the proteins needed for viral translation. The translational machinery of the host must be hijacked to allow for viral protein creation. Because of this, the virus does not need to code for a large number of proteins as it can use the host's machinery. Influenza has its genome make three distinct types of proteins. The first type is the outer membrane proteins which are used to attach to the host cell and start endocytosis. The second type is RNA polymerases, the proteins that allow for transcription, and third are the Matrix proteins. Matrix proteins assist with the hijacking of host machinery.

Viral RNA replication does not have a checking mechanism when replicating their genome and therefore experiences frequent mutation. One type of mutation that occurs is point mutations, or single alterations in the virus's genetic code made by either adding, deleting, or shifting what parts of the RNA is made into proteins. These mutations become one of the best mechanisms for defense against the immune system, as the change in viral proteins leads to the immune system having a harder time identifying the virus as a threat when the proteins that the immune system must identify changes. Another major part of viral subterfuge of

the host's defenses is the use of multiple sources of virions when creating new viral particles. This ensures recombination of material and more unique viral characteristics (Muramoto et al. 2005).

During the course of a viral infection, many viral RNA strands are created. Some come from different virions and therefore have unique sequencing and some are unique due to mutation during replication. This leads to packaging of the daughter virions to be made recombinant of the virions that first arrived at a cell, and ensure that the virus that emerges has a better chance of evading the immune system. The viruses are able to do this by using their non-coding region as identification points. Additionally, they have a higher probability that the RNA put in each new virion is unique, and therefore able to avoid detection longer. This hiding allows the virus to be able to be transferred either to more new cells in the host's body, or be transported by fluids to a new host to begin the cycle in a new location with an unsuspecting immune system. These multiple sources of alteration are why the influenza vaccine is done yearly, as each year genetic drift and point shift lead to a recombinant virus that both has specialized unique features and is unknown to the memory cells of the immune system.

Time Period of Pandemic

The influenza virus strain came into the human population at a very difficult time in world history. In 1918, the war that was expected to "end all wars" was raging in Europe. This began in 1914 and was caused by a plethora of economic, political, and militaristic reasons. The alliances fighting the war had significant control over their own areas as well as their colonial holdings, leading to a full scale global conflict. When the United States entered in during 1917, a global migration had occurred to move goods and people from many sections of the world into Europe. With the boom of people and goods moving internationally, diseases were easily transferred. This is because when two previously isolated groups engaged in close interaction, diseases were often spread to hosts who lacked immunity (Humphries 2013).

Additionally, the United States wartime mobilization aided in the spread of influenza. Within the military bases, transport ships, and the trenches where the war took place, personal space was at a minimum and many men were forced to live in conditions that allowed diseases to transfer. The lack of hygienic conditions was paired with a lack of knowledge of what the disease causing agent was and how to prevent it, or at least minimize its effects. Influenza would not be known as a virus until 1933 (Billings 1997). Individuals were woefully uneducated on the virus, and because of their ignorance, along with the diverted attention and heightened stressors within a warring nation, influenza quickly spread until it could not be contained. As the war waged on, countries desperate for their citizens' support began using mass propaganda and censorship, leaving many people oblivious to the severity or proximity of the pandemic to their location. As a result, the virus snuck up on its unsuspecting victims, and quarantines, which effectively combatted other epidemics, were not used stringently. Cities were unwilling to lessen their war output for the safety of their people, and their failure of action lead to millions of civilians falling victim to the disease (Humphries 2013).

Approach

The H1N1 strain of influenza had many specialties that lead to its rapid and repeated spread across the globe. The

pandemic can be credited to both environmental and internal factors; there was widespread migration of people and animals to new locations, and it was different in genetic makeup than any preceding influenza strain, causing a novel immune reaction as a result. These factors allowed the virus to successfully take down young adults, a rare target. Young adults are historically more successful at fending off diseases, but at this time in history, they were the crowd most likely to be travelling, therefore providing to more hosts for the virus. The death toll was so astronomical because the H1N1 strain exhibited commensalism with a bacterial pneumonia, allowing the bacteria to infect hosts weakened by the virus. This was the final straw that solidified the H1N1 virus to be so destructive (Chein et al. 2010).

Virus's Start

The origin of this virus has been argued to have started in China, the United States, or southern England. These theories all try to trace the virus to better understand why the virus acted like it did. When the outbreak originally began in the fall of 1918, many people believed that it was started in Spain. Spain was one of the few neutral areas during the war and therefore had a non-censored press that reported the spread as well as the up to 8 million deaths in May of 1918—one of the first major reports of the infection's unusual potency (Billings 1997). The newest and most respected source has the virus emerge from China in the winter of 1917. Original reports from this time from China indicate their "winter illness" had a similar death toll and appearance to the infection that would ravage the globe (Humphries 2013). Another major reason this is considered a major source is the humid conditions that the virus originated in. During the virus's travel around the world, the areas that had the highest death rates were humid and warm locations (Billings 1997). It is more logical that the infection developed in a similar area, since the United States lacks the humidity and southern England lacks warmth.

The first known large scale reports of the virus do start at isolated military bases, but this is more due to the fact that many doctors were in the service and therefore the military had better medical records being kept. The United States at this time in early 1918 was in full military mobilization mode with heavy censorship. Many believed that it would be traitorous to the war effort to raise a panic about the deadly virus, since people would respond by isolating themselves for safety during a time in which the country required mass production. By keeping the spread of the illness in secrecy, there were over 600,000 deaths by the time herd immunity was established (Billings 1997).

As soldiers crossed borders and continents, the H1N1 virus was able to capitalize on the new range of hosts that many diseases could not access. As a result, multiple waves of the virus developed due to the ability to evolve while continuing to find susceptible hosts. The main case for finding the source of the virus however, comes in the form of the shipment orders of the Oriental work force. They moved across the Pacific Ocean into North America and then across the Atlantic into England to support the war effort, since the war blocked the Eurasian path to England. The virus was able to land on each continent with the arrival of the Chinese labor force (Humphries 2013). This proverbial nail in the coffin, helps to put to rest the origin question.

However, the way the virus that was able to come through many locations three times in one year must be looked at more

closely. The environment for a pandemic gave rise to the traveling ability, but the virus was able to continue to fool new immune systems to continue its march of destruction. To find how the virus was able to completely avoid so many people's immune system the genotype of the virus must be examined.

H1N1 Genome

The H1N1 virus was so widely effective because the world population lacked herd immunity, which would have limited transmission by limiting the number of available hosts. This assisted in the transfer of the disease, but new alterations to the viral genome allowed for more subterfuge as it had never before been seen by the host.

These adaptions come from two major sources. First, a shift in the reading frame of one segment of the RNA lead to the transition of PA (part of the virus's polymerase complex) into PA-X, a mutation that lowers the pathogenicity of the virus in a way that limits the initial immune response of the host (Jagger et al. 2012). This unique way for the virus to use its small genome to create more protein types allowed for the virus to mutate further than the original 13 major proteins the virus uses (Jagger et al. 2012). This is proven to be true in the case of the H1N1 strain, which was able to go through such a wide transformation from the original strain that was observed in the summer of 1918, to the more deadly second strain. Those who were infected in the first wave were still susceptible to the second wave. This phenomenon is rare in pandemics, as usually people susceptible to the disease either die off in the first wave or become immune after their immune system fights them off.

Looking at the mathematical models of the disease spread, only 1 in 10 infections were symptomatic, leading to the idea that the PA-X was the cause. PA-X limited not only public health responses, but also the body's own defenses (Bolton et al. 2014). However, this virus was not just novel in its way to produce new proteins; it was able to infect the same hosts by using the same PA-X protein coded for and spread by the first wave. This rare feature was due to influenza's rare recombinant nature, in which it attempts to become completely pathogenic after a certain point in the infection. The ability of the virus to almost mimic quorum sensing of bacteria is not fully understood, but could be either purposeful or just a statistical anomaly due to enough trials of recombination due to mixing of virus RNA. This needs to be explored in greater detail, as no confirmed hypothesis exists at this time and interactions between virions to work as a group has not been well documented in past studies (Jagger et al. 2012). One thing is for sure: the H1N1 strain of virus, when fully potent without PA-X, was able to wreak havoc on the body in ways never seen before.

Cytokine Storm

As described previously, the immune system's way of interconnecting and specializing their attacks is based around the proteins known as cytokines. Their ability to ensure proper immune response makes them one of the immune system's most important pieces, but also one of its biggest weaknesses if able to be hijacked. This is evident in the virus's ability to incapacitate and kill the 20-40 year olds that usually survive such infections. It is hypothesized that the cytokines were used at a normal level during an influenza infection prior to this outbreak. This means

this age group's first exposure to influenza occurred well before the 1918 strain.

The exposure to another strain of influenza led to this strain's ability, by an unknown mechanism, to cause a cytokine storm by over expressing the cytokines and causing system-wide damage and immune paralysis (Shanks et al. 2012). As a result, those with the strongest immune system became the most susceptible to death, as the virus used the elevated level of the cytokines to make the body self-harm and therefore softened its ability to fight off any infection. This is similar to an allergic reaction, when the body fights the very thing it is supposed to be protecting. Such a storm allowed for the body to be susceptible to secondary infections that characterize the death rate that was associated with the second wave. The mixing of viral genomes led to the most deadly single disease wave in human history (Billings 1997). This influenza strain although very easy to transmit was not the main killer that led to the wide spread devastation. If the influenza virus was just weakening many people what was the true killer? That honor is held by bacteria pneumococcus.

Pneumococcus

It is known that many microbes live together and exhibit symbiotic relationships. But when two pathogenic species use their abilities together the host is unable to survive. This was the issue with the symbiotic relationship of the H1N1 strain, and pneumococcus. The virus was able to cause system wide damage by over expression of certain signaling molecules. This leads to the initial site of the viral infection (the lung epithelial tissue) to become very vulnerable, as those cells are already weakened and unable to fight off the growth of pneumococcus. The H1N1 virus was found to not to be the major cause of death, as most deadly infections seemed to occur following a short period of grace at the tail end of the viral infection, before the bacterial infection was in full force (Chein et al. 2010).

Pneumococcus, being bacteria, is able to live and exist without a host. This is different from influenza, which needs to live inside the host cells to survive. The difference in organisms lies within the key fact that the bacteria does not go inside of the lung tissue, but rather grows on top of it, secretes toxins which breaks down the lung tissue, and takes up nutrients from those cells. The Pneumococcus, while breaking down the tissue, causes fluid to fill the alveoli of the lungs and increase swelling as the immune system tries to fight the disease. Since the alveoli are the respiratory surface, this action reduces the body's oxygen supply (Billings 1997). Victims often turn the blue, as was the case in many of the fatal accounts of the 1918 pandemic (Billings 1997). The body tries to remove this fluid and the colony of bacteria by coughing up the phlegm, but this cannot always be done. Once the fluid can't be cleared fast enough, the fluid builds up and further restricts oxygen intake until the victim suffocates. Death came quickly to these individuals, as the body's defenses were weakened by the virus and unable to combat the new attacker. Evidence for this causality is not only supported by the studies indicating that Pneumococcus vaccine reduced the number of deaths caused by influenza (Chein et al. 2010), but also by the fact that the most common areas on the globe where death occurred were humid warm locations that are prime areas for bacteria to grow and prosper (Humphries 2013).

Conclusion

Although mysterious in origin, the 1918 H1N1 strain of influenza is known as a black mark in history, causing the single largest medical tragedy in recorded human time. This virus was able to capitalize on a political situation that called for interactions among people in higher numbers than ever before from many corners of the globe. The need of globalized trade due to the war allowed the virus to spread and not be contained after just one wave. The virus was able to sneak up on its victims due to its novel genetic shift that made the virus able to quickly spread through the population and weaken the immune system of its host before he was aware he was sick. This gave the H1N1 strain time to recombine with other viral strains as well as do point mutations, which allowed the virus to mutate within the human host while continually being spread. It was able to exist in its normal PA form, causing a cytokine storm and damaging body's system-wide. It was most fatal to people aged 18-40, who normally do not die during the course of an influenza outbreak. The phenotypic peculiarities exhibited by this strain of influenza led it to be so destructive. The virus used the body's own immune system as a weapon against its hosts, which allowed the virus to accumulate significantly more drastic death rates. The combination of an asymptomatic period early in the infection, combined with an increased number of susceptible victims due to human migration during war time, lead to such a vast number of victims of the disease. Once infected the combination of cytokine storm and bacterial secondary infection led to deaths at a higher rate than ever before seen in a human pandemic. This viral strain is still studied today, because its genotypic alterations are just now 100 years later being completely understood and with that understanding comes the ability to know why this viral strain was different from other influenza strains, and why it was able to kill in a pattern unique to other infections.

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