The Study of a Pandemic

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"I had a little bird
Its name was Enza
I opened the window
And in-flu-enza"
--Children's Skipping Rhyme, Spanish Influenza Pandemic of 1918

It is an old rhyme that describes the situation in the 1918, during the first wave of influenza pandemic. What started as a mild common cold soon spread worldwide, killing an estimated 40 million people and shattering the previous notion that the flu was not a mortal illness (Pandemic). The results were devastating. The pandemic killed more people than World War I, and more people than 4 years of the Bubonic plague. (Molly Billings, 1997) Since, two other influenza pandemics have occurred: the 1957 Asian Influenza and the 1968 Hong Kong Influenza. While both were terrible, the 1918 influenza has been the only flu pandemic associated with mortality measured in 1000 per 100,000 population (Belshe 2005).

On October in 1918, something unusual happened after the Cedar Rapids Swine Show held in Iowa. Most of the pigs at the show were infected with a respiratory disease that was similar to the seasonal flu experienced at the time by humans. Occurring at the same time as the human influenza pandemic, it was widely believed that the virus had adapted to the pigs. It was not until 1931, however, that this was proven when Robert Shope, a veterinarian, infected healthy pigs by transmitting the virus containing secretions from sick pigs. Shope`s next experiment showed that the serum from adults could neutralize the swine influenza virus strain. He further went on to prove in 1931 that secretions isolated from almost everyone who was older than 12 years protected the mice from challenge with the virus isolated from the pig in 1930._These experiments showed that a virus anitigenically similar to the pandemic virus had been in the human population and had origin in the 1918 pandemic strain. (Shanta M. Zimmer and Donald S. Burke 2009)

So, when the news of the swine flu broke out in April 2009, the fear was palpable. Soon "swine flu" was the buzz word in international health and travel. Globally, it has been responsible for more than a hundred thousand confirmed cases and about eight hundred deaths (World Health Organization 2009). This article will aim to understand the basics of H1N1 virus and how it affects humans: the path physiology and the pharmacology involved in treatment.

What is Swine Flu?

"Flu" refers to the contagious respiratory illness caused by the influenza virus. The influenza virus belongs to the family Orthomyxoviridae and is a RNA virus. It has three genera: A, B and C. Genus A is responsible for pandemics though all three can infect humans. The virus particle is 80 to 120 nanometers in diameter and spherical in shape (ICTVdB Management 2006). The structure of the virus is shown in Figures 1 and 2.

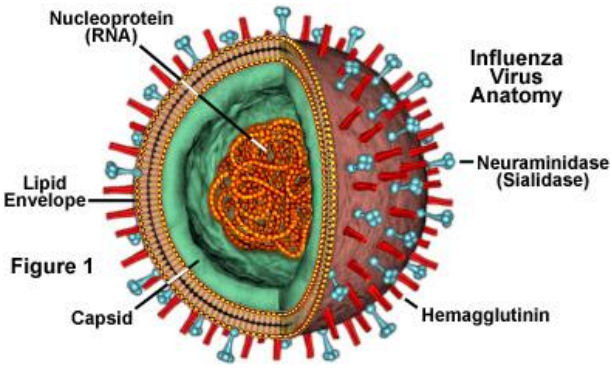

Figure 1: Structure of Influenza virus

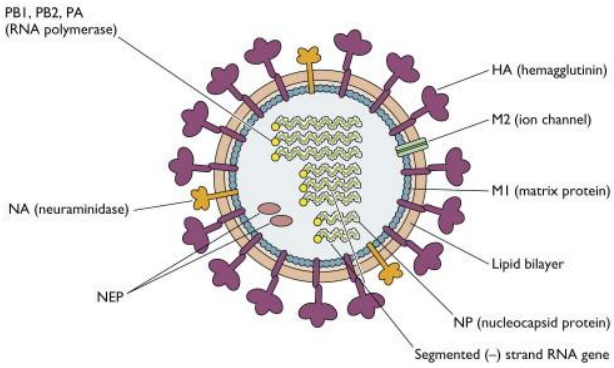

Figure 2: Structure of Influenza Virus (simplified)

The viral envelope contains two main types of glycoproteins: hemagglutinin (H) and neuraminidase (N). Hemagglutinin anchors the virus to any cell it seeks to enter while neuraminidase helps the invading viruses to digest their way through mucous secretions as they approach the host cell (Watts 2009). These

proteins are responsible for adaptation of the virus to a host cell and often are responsible for generating antibodies that are directed against them. The hemagglutinin comes in 16 structural subtypes and nine types of neuraminidase. The nomenclature of the influenza virus is based on antibody responses to these glycoproteins. The avian influenza A virus is H5N1. The 'swine flu' virus is H1N1 influenza A virus. It was originally termed "swine flu" virus because initial laboratory testing suggested that the genes of the novel virus are very similar to the genes normally found to pass amongst North American pigs (CDC 2009a). But further study has disproved this notion, and it is now appropriately called as novel H1N1 influenza virus or simply, H1N1.

Evolution of influenza virus

The 'swine flu' virus is related to the 1918 H1N1 influenza virus (Zimmer and Burke 2009). In fact, all of the influenza A pandemics that we have experienced since 1918 and nearly all cases of influenza A worldwide have descended from the 1918 Spanish Influenza pandemic (Morens). However, while related, they are not the same virus. Over a period of time, influenza viruses undergo remarkable changes in structure by means of mutation, known as "drift and shift," or through "genetic reassortment." (Morens, Taubenberger and Fauci 2009) If two viruses infect the same cell, they may exchange their genetic material during replication in a process known as reassortment. Moreover, reassortment can occur between viruses that infect different species. Because of this reassortment, new varieties of viruses are continuously produced, the process of which is exhibited in Figure 3. Because the human immune system has never been exposed to these novel strains, it is possible for it to become overwhelmed, resulting in prolonged illness, more severe symptoms than the seasonal flu, and, in some cases, death.

The current novel H1N1 virus has two genes from flu viruses that are usually found in pigs in Europe and Asia, in addition to avian genes and human genes. Hence, scientists also call the H1N1 virus a "quadruple reassortant" virus (Center for disease control and prevention 2009a). Therefore, although the influenza virus of 1918 pandemic and the current 'swine flu' virus are both H1N1, but they are different in terms of the amino acids that make up their hemagglutinin proteins and the genetic material they contain. The 'swine flu' virus is the strain S-OIV of the H1N1 Influenza virus (Zimmer and Burke 2009).

How severe is the current H1N1?

The influenza pandemic in 1918 had a case fatality rate of 2.4% (,Jeffery K. Taubenberger and David M. Morens,2006); pandemics occurring afterwards had lesser case fatality ratios. In general, death due to influenza epidemic is often less than 0.1%. The Center for Disease Control and Prevention reports that complications resulting from seasonal viruses cause around 36,000 deaths in a year in the U.S. and are responsible for around 200,000 hospital admissions. Initial data suggests that the current H1N1 virus is relatively mild, with a case fatality ratio around 0.5%, similar to the upper range of that seen for seasonal influenza (Garske et al 2009).

The proposed marker of pathogenicity of H1N1 virus is a coding sequence for the smallest of the viral proteins, PB1-F2. This sequence was present in the viral strains causing the Spanish Influenza pandemic of 1918 in addition to the pandemics of 1957 and 1968, but is missing in the current H1N1 virus (Wang and Palese 2009). However, there are some aspects of the current H1N1 virus which makes it more aggressive than the usual seasonal flu virus. Recent studies have shown that the H1N1 virus causes more severe infection in the lungs than is expected from a seasonal flu (Itoh et al 2009). It has been known to cause severe illness, acute respiratory distress syndrome, and death in previously healthy young-to-middle-aged individuals (Perez-Padilla et al 2009).

Dr. Jonathan Yewdell, MD,PhD, of the National Institutue of Allergy and Infectious Disease, National Institutes of Health (NIH), says that while the flu does not currently appear to be as severe as some others, it could potentially exhibit a high pathogenicity due to the lack of immunity amongst people against the virus responsible for the swine flu. "There is little existing immunity to the swine origin influenza virus (SOIV)," said Dr. Yewdell. "The transmission rates are likely to be extremely high. Currently circulating strains seem to be of relatively low pathogenicity, but this can change with just a few mutations."

Mirroring the concerns of Dr. Yewdell is Artealia A. Gilliard, representative from the Centers for Disease Control (CDC). "There is merit behind concern for novel H1N1," she states. "This is a mild to moderate disease that is spreading illness rapidly from person to person. It has caused a range of illness, and in some cases, death."

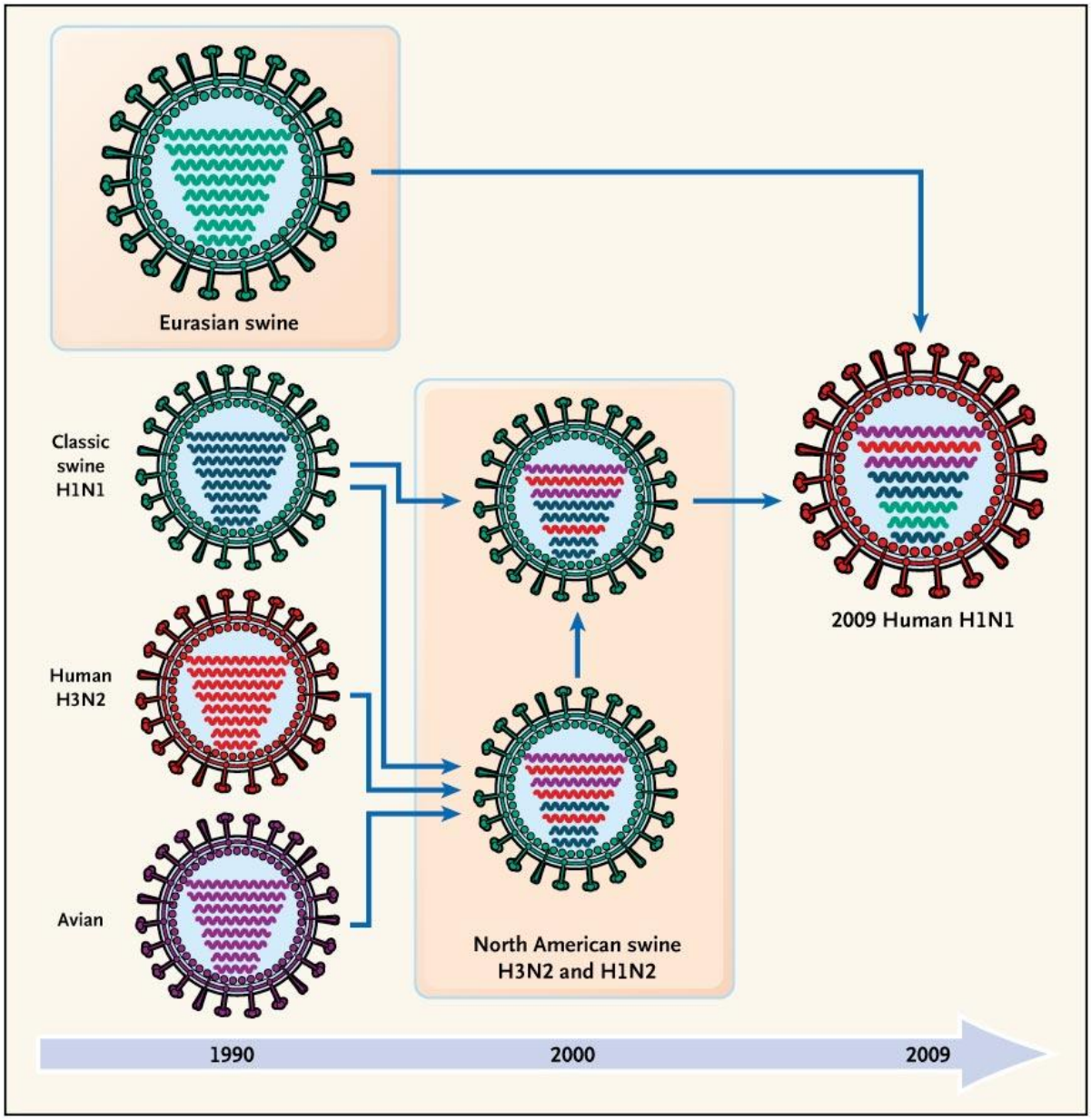

Figure 3: Reassortment of influenza virus

Symptoms and the at risk population

The symptoms of infection with H1N1 virus is similar those of the seasonal flu. Fever, cough, sore throat, runny or stuffy nose, body ache, headache, chills, and fatigue occur in most patients, and few may experience diarrhea and vomiting (CDC 2009a). The danger signs of the illness in both adults and children include difficulty breathing, persistent vomiting, and flu-like symptoms which resolve but are replaced by fever and a worse cough. In most cases, the symptoms resolve within a week or so after the illness. As a general rule, viral infections and their severity are more common in people with weakened immunity; hence, children less than 5 years old, elderly people older than 65 years, and often pregnant women are expected to fare worse than others. In addition, people with pre-existing medical illnesses such as asthma and diabetes have worse symptoms. Health care professionals who may be in direct contact with the flu patients are also at risk. However, the age group at risk in terms of mortality for the current H1N1 virus is between 5 and 64 years of age, which is in contrast to that which is normally seen in seasonal influenza, where an estimated 90% of influenza-related deaths occur in people 65 years or older. Figure 4 shows the mortality rates observed in different age

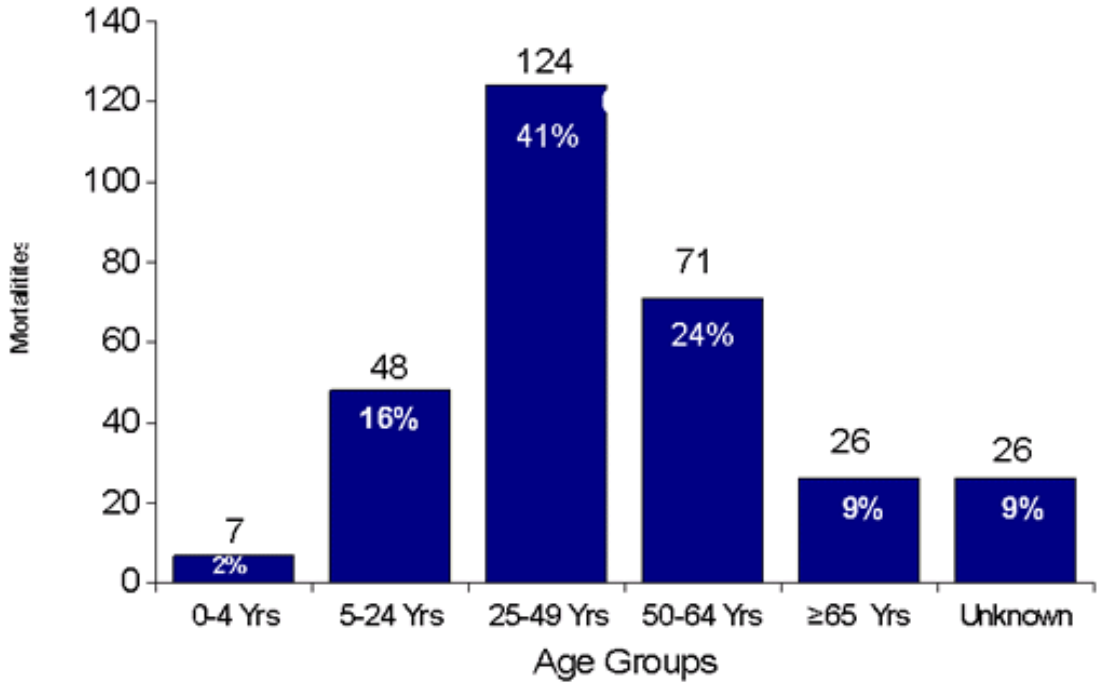

Figure 4: Age-wise mortality in patients infected with novel H1N1 influenza in United States among 268 patients.

groups amongst 268 patients studied in United States (Center for disease control 2009c).

In addition, with the current H1N1 virus, pregnant women are four times more likely to be admitted to a hospital due to severe H1N1 disease than the general population (Jamieson et al 2009). The mortality rate is also higher in pregnant women. These infections in women can also lead to preterm births, anomalies and abortions (CDC2009d). Obesity (BMI>30), not recognized as a risk factor in other forms of seasonal influenza, is seen as a risk factor for developing flu- related complications in novel H1N1 influenza infection. The exact cause is unknown.

The different group affected has not gone unnoticed by the CDC, whose representative notes the similiarities between the age patterns of the 1918 virus and the current H1N1 virus. "The 1918 virus seemed to have disproportionately affected people between the ages of 5-14 - they had the highest infection rates, but the lowest death rates. Similarly, people under the age of 25 have seen the most illness and hospitalization, but have low death rates as a result of the 2009 novel H1N1 virus. We still don't know why the 1918 virus affected so many young people, and we don't yet know why the 2009 virus is doing the same." Ms. Gilliard also states that those who are over 65 and exhibit some immunity to the virus may do so due to exposure to the similar 1957 pandemic flu virus. "The evidence suggests the possibility that older groups may have had some immunity from the virus, probably from exposure to a similar virus….This flu virus is unique because it is causing wide-spread illness outside of the normal flu season, and it seems to be affecting certain groups more than others - for example, 50% of the people who have been hospitalized as a result of novel H1N1 are under the age of 25. If people over the age of 65 are immune to novel H1N1, it might be because of exposure to the 1957 pandemic flu virus, which had some similar antigenic characteristics to the 2009 flu…But there are lots of other possibilities, so we don't know for sure."

According to Dr. Yewdell, the observance that the current H1N1 virus affects a different age group than does the regular seasonal flu may be due to differences in existing immunity to the virus. "Some of the age-related difference are likely due to differences in existing immunity," he asserts. "Some are probably due to differences in innate immunity. Age generally decreases immunity across the board." Dr. Yewdell states the goal for this current H1N1 virus is to vaccinate children, with the aim to make more people immune to the disease and therefore more resistant to catching and spreading it, known as "herd immunity." "Current thinking is that children provide a critical reservoir and vehicle for spreading epidemic flu—

the idea is to vaccinate them (they also respond to vaccines better than the elderly) to provide herd immunity," Dr. Yewdell explains.

Spread of the virus, immunity and prevention

The spread of the H1N1 flu occur in the same way as the seasonal flu: through droplet infection and through direct contact. The infectivity period is believed to be a day before the symptoms develop and seven days thereafter (Center for Disease Control 2009a). Despite the popular name of "swine flu," the H1N1 strain has less to do with swine than initially thought. The disease is transmitted like any other flu, and, hence, is not transmitted by eating pork meat. Since the virus is already pandemic, it is important that people practice essential and effective basic hygiene measures, such as hand-washing for 20 seconds with hot and soapy water, not re-using tissues, and properly disposing of tissues (O'Dowd 2009). Covering your mouth and nose while sneezing is extremely important, and it is advisable to use alcohol-based hand cleaners, especially after coughing and sneezing, to both protect yourself and avoid infecting other people. In addition, avoiding contact with other people 1 week after the illness can greatly decrease the chance of infecting others (CDC 2009a).

While experts agree that it is better to avoid coming in close contact with people with symptoms of the flu, some have decided to take a different and expert-deposed approach by holding "swine flu parties." These "parties" are gatherings in which people who are not yet infected with the H1N1 flu come in close contact with those who do have the flu in hopes of catching a milder, less dangerous form of the virus and thus the immunity that will come afterwards, as opposed to catching the virus later on in the year, when it may have increased in severity. While maybe shocking at first, this approach of pre-empting the more serious form of a given illness and building immunity on the milder form has been utilized for years with illnesses from smallpox to the chicken pox. Experts have vehemently spoken against this method for the current H1N1 virus, as it cannot be predicted if the resulting infection will be mild or severe. Ms. Gilliard, CDC Representative, speaks strongly against these "parties." "Novel H1N1 can cause a range of illness - from very mild, in which people get better on their own, to severe, in which people require hospitalization or die. Each person is different and is affected by the influenza virus differently - trying to catch the disease on purpose is very dangerous, and could be deadly." The Center for Disease Control (CDC) has officially recommended against holding swine flu parties, stating:

"CDC does not recommend "swine flu parties" as a way to protect against novel H1N1 flu in the future. While the disease seen in the current novel H1N1 flu outbreak has been mild for many people, it has been severe and even fatal for others. There is no way to predict with certainty what the outcome will be for an individual or, equally important, for others to whom the intentionally infected person may spread the virus. CDC recommends that people with novel H1N1 flu avoid contact with others as much as possible. They should stay home from work or school for 7 days after the onset of illness or until at least 24 hours after symptoms have resolved, whichever is longer." (Center for Disease Control, 2009a)

Treatments

Antiviral drugs Oseltamivir and Zanamivir are currently recommended for the treatment of novel H1N1 infection. They reduce the duration of the illness and prevent serious complications.

Both Oseltamivir and Zanamivir are what scientists call "neuraminidase inhibitors." They work by inhibiting the activity of neuraminidase, which is a glycoside hydrolase enzyme that works on neuraminic acids by cleaving their glycosidic linkages. By cleaving these linkages, viral neuraminidase allows the virus to penetrate cells. By inhibiting the activity of viral neuraminidase (a common goal for preventing flu infection), these two treatments prevent cellular infection by the virus. Inhibiting neuraminidase also decreases the probability that the illness will occur and the severity of the illness should it develop, due to the fact that neuraminidase is also responsible for efficient spread of the virus and the intensity of the illness. (Couch 2000).

While there is great promise for these vaccines, there have been reports of resistance. Reports have suggested that the virus is resistant to Ostelamavir in most of the parts of Norway, whereas it is susceptible to this drug in parts of Japan. Ironically, Japan has one of the highest per-capita usages of the antiviral drug Ostelamavir, while in Scandinavia it is rarely used (Kent A .Sepkowitz, 2009). This interestingly odd pattern goes against the notion that drug resistance is normally parallel to drug overuse. The CDC representative states that while it's true that a flu virus may be resistant to one antiviral, it does not mean it will be resistant to other antivirals. "Influenza is very unpredictable, and the virus is constantly evolving and moving forward. Some of these changes can result in

viruses being resistant to one or more of the antiviral drugs that are used to treat or prevent them. The good news is that so far, influenza viruses that are resistant to one antiviral, are not resistant to all antiviral. A major part of the CDC's flu surveillance program is to test the different influenza viruses circulating in a particular year and to determine which antiviral is the best fit." In this regard, vaccines when available will be of great use in preventing the acquisition of the H1N1 virus.

With regards to a perhaps common misconception, the available seasonal flu vaccine does not protect against novel H1N1 influenza infection. Dr. Yewdell states that this current H1N1 flu is from a different lineage of flu, and therefore the regular seasonal flu vaccine will not "cover" the H1N1 flu, and people should get vaccinated if they can. "The HA is from a different lineage. There is little antigenic cross-reactivity between SOIV HA and current HAs…they probably diverged more than 50 years ago." Stating that he believes a vaccine generated with the SOIV HA would be effective, Dr. Yewdell also notes that a vaccine against the current H1N1 virus will have to focus on its comparative antigenicity—or ability to evoke an immune response—with other current flus. "The key to vaccines is matching the antigenicity of the vaccine with the circulating strains," he states.

Dr. Yewdell finally advises: "Get vaccinated if possible." Ms. Gilliard concurs, suggesting that people visit the CDC website (www.cdc.gov) in order to find detailed information on how to protect themselves from the flu: "Check the CDC website for tips on how to prevent the spread of flu….cover your coughs and sneezes, wash your hands with soap, avoid touching your nose and mouth, and to stay away from sick people. And if you fall within the recommended groups - get the seasonal and novel H1N1 vaccines as soon as they become available."

A vaccine for novel H1N1 influenza is expected in the United States by mid-fall of this year—Ms. Gilliard of the CDC says, "We hope to have a vaccine ready in October." She also stresses that, "the CDC's Advisory Committee on Immunization Practices has recommended that people younger than 25 receive the novel H1N1 vaccine as soon as it becomes available." Initially, it is planned to be given to the population that is at a higher risk of developing serious complications. These groups include pregnant women, people who live with or care for children younger than 6 months of age, health care and emergency services personnel with direct patient contact, children 6 months through 4 years of age, and children 5 through 18 years of age who have chronic medical conditions (CDC 2009b).

Conclusion

The novel H1N1 influenza virus is spreading through many countries around the world, and the number of cases is increasing every day. According to various reports in different parts of the world, the disease might not be as bad as initially feared. Still, this is something that will not be known for sure until much later, and it is important for people to continuously monitor this virus and for the scientific community to regularly look for any mutation or reassortment in the current H1N1 virus. A high level of preparedness is necessary to prevent a high mortality occurring from a sudden change in pathogenicity of this virus. What are the mechanisms that causes these changes, the factor related to infectivity, transmissibility and or the sheer audacity of these primitive forms to challenge the higher or developed human race appears to be complex and poorly understood. Perhaps the facts that not long after the world had contained the Avian Flu, another type of Influenza had slipped under the radar, across the boundaries causing mass hysteria is bewildering enough. But even if it is the descendant of the 1918 pandemic virus ,we have to believe that we have come a long way from the innovations and facilities that were at disposal to the mankind in 1918, and the virus might not wreak as much havoc as the initial wave of Influenza did in that fateful year of 1918.

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