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MIRAD Laboratory Presents:
Influenza Data Center

An Interactive Qualifying Project

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a Bachelor of Science

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Abstract

Influenza has impacted millions of people worldwide for a number of years. Every year influenza viruses continue to disrupt the lives of many people. The frequency of hospital visits is now becoming substantial as a result of influenza related illnesses. By the estimates of the World Health Organization, the pandemics of the 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong (H3N2) and more recent 2009 Swine flu (H1N1) are among the most impactful presentations of influenza. Influenza viruses increase the risk of pneumonia, cardiopulmonary, acute respiratory and other diseases. Health vulnerabilities and mortalities associated with influenza continue to be a major concern for healthcare providers. In each influenza season, healthcare providers, public health departments and governments focus on communicating influenza awareness and preventive measures. Influenza is classified into A, B and C viruses, and there is evident indicating that the viruses continue to experience genetic changes. The influenza A and B viruses account for most of the serious health cases in humans. The objectives of this Interactive Qualifying Project (IQP) are to provide an influenza data presentation, evaluate the historical impacts of influenza and propose effective ways for influenza awareness. Sanitation, hygiene, and clean environment coupled with public health education are common preventive measures of influenza. Vaccinations are also available and governments around the world encourage their citizens to be vaccinated against influenza. New vaccines and treatment options are continuously being developed to reduce the spread of influenza within communities. The number of people receiving vaccination is growing worldwide. Self-presentation, prehospital and clinical presentations are common methods for diagnosing influenza. The goal of these diagnostic presentations is to report the onset of influenza in a patient. Molecular biology has speed up the process of diagnosing influenza. Polymerase Chain Reaction (PCR) is one of the rapid point-of-care testing methods for influenza. A rapid diagnosis of influenza enhances the scenario of locating most effective treatment. It can reduce the spread of flu, prevent exposure to healthcare workers, and mitigate complications for infected individuals. The proposed influenza data presentation describe effective ways for preventing, diagnosing and treating influenza. Direct contact, indirect contact and noncontact are presented as modes of transmitting influenza from an infected patient to other people. The social impact of this IQP is that the proposed influenza information data is made available through a web internet platform (www.MIRADlab.wpi.edu). A number of literature dealing with influenza is reviewed to particularly emphasize the history of influenza outbreaks, modes of transmission, preventive measures, diagnosis and treatment. The website mentioned previously, provides an influenza threat level map by state along with CDC advice as to how to prevent the spread of influenza. Lastly, the website presents information about influenza history, modes of transmission, preventive measures, diagnosis and treatment. By presenting this information in one place, the IQP is successful in building an Influenza Data Center (IDC) where the general public can get information about influenza.

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Disclaimer

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Chapter 1. Influenza Disease Solutions: Influenza Data Center (IDC) Library

1. Introduction

There are three main influenza viruses and they are classified as A, B and C viruses. Influenza A and its own virus classifications (H1N1, H2N2, H3N2, H5N1 and H7N9) are known to cause more severe health conditions than influenza B and C viruses. Pandemic influenza is usually associated with influenza A and B viruses. Influenza C virus has limited occurrence in influenza outbreaks. Historically, there had been influenza pandemics during which millions of people perished by influenza related illnesses. Influenza is a virus that is infections and can spread through direct contact, indirect contact and noncontact with people suspected of influenza, people infected with influenza and people infected and symptomatic with influenza. Noncontact is spreading influenza virus in airborne, person to person contact is direct contact and person to object (such as a door handle, table or bench) is indirect contact. National governments and healthcare providers worldwide consider influenza viruses and their accompanied illnesses as public health emergency threats. Each year in the United States, influenza viruses continue to cause influenza related illnesses. Since 2010, the Center for Disease Control and Prevention (CDC) estimated that the number of influenza related illnesses exceeded over 500,000 patients across in the United States. As the influenza viruses continue to evolve, the number of influenza cases also continue to fluctuate. There are growing efforts to locate effective ways to fight against influenza. The current fight against influenza are five folds and they are: (1) developing preventive measures through vaccination, therapeutics and public health awareness, (2) educating the public about the modes of transmitting influenza, (3) reporting self-assessment, prehospital and clinical presentations of the onset of influenza-induced symptoms to health providers, (3) quantifying the onset of influenza symptoms in patients using rapid point-of-care testing (POCT) devices, (4) isolating (i) people suspected of influenza, (ii) people infected with influenza, (iii) people infected and symptomatic with influenza

and (5) planning treatment options for influenza carriers. These five folds will help to develop predictive models of influenza pandemics. Since 1938, influenza vaccinations and therapeutics have been the healthcare standard for preventing the viruses. Every year in the United States the number of people receiving vaccination is increasing. In 2016-17 flu season, 46% of US population received the flu vaccine. This was an increase of 1.2% from the 45.6 % of the segments of the population who received vaccine during the 2015-2016 flu season.

The risk of becoming infected and symptomatic with influenza is high in segments of the population with weak immune systems. Mortality in these vulnerable segments of the population is high and recovery of influenza infected individuals is long. Without immediate intervention and treatment for high risk segments of the population, the spread of the influenza virus to other susceptible individuals increase. When individuals are infected with influenza, they typically experience a variety of onset of symptoms including sore throat, fatigue, muscle pain, fever or body chills and a cough. Early reporting of the onset of influenza-induced symptoms to healthcare providers support immediate interventions and plan for suitable treatment options. The objectives of the interactive qualifying project is to develop an influenza data presentation library. The IDC library is created to provide greater awareness of preventive measures against influenza, modes of transmitting influenza, assessment and diagnosis of influenza, reporting the onset of symptoms of influenza and seeking treatment options in a timely manner. The proposed IDC library also encompasses the history of influenza outbreaks, an index of onset of influenza symptoms and point of care testing devices. The polymerase chain reaction, known as PCR, is the widely used POCT device for molecular diagnosing of influenza. The PCR and its different molecular variations are known to provide real time testing of influenza A, B and C viruses. We discuss the process of collecting samples and testing samples using real time PCR. We use the yearly collected CDC data to develop color-coded risk assessment maps of influenza for the United States and provide updated influenza information from CDC. A website is developed to provide a worldwide access to the IDC

library. The name of the website for the IDC library is www.MIRADlabs.edu. Healthcare providers and national governments around the world are adopting innovative surveillance methods and public health education to prevent influenza pandemics. We discuss the continuous threats of influenza, challenges facing healthcare providers and some of the innovative ways to isolate people suspected with influenza, people infected with influenza and people infected and symptomatic with influenza. The societal impact of this IQP is that the proposed IDC library supports the effort of early reporting of the onset of influenza-induced symptoms, interventions and planning of treatment options for individuals infected with influenza.

The remaining part of the project is categorized as follows. In Chapters 2, we describe historical outbreaks of influenza and their accompanied impact in terms of deaths and illnesses. From the 1918 Spanish flu to the recent 2009 Swine flu and now, we present graphs and tables to describe the adverse impact of influenza on the segments of the population. The first part of our analysis is to understand the data collected during the outbreak periods from 1918 to presents as they relate to Mortalities and influenza related illnesses. The second part is to present the data in a form consistent with the developed IDC library. The construction of the IDC library and its content is presented in Chapter 3. The threats of influenza highlights the need for effective preventive measures, vaccinations, and therapeutics and public health awareness of the modes of transmitting influenza. Chapter 3 contains a number of diagrams and context to promote a public health awareness of influenza and benefits of early detection of influenza. The diagrams are used to communicate preventive measures against influenza, modes of transmission, the onset of symptoms and treatment options. The conclusion in Chapter 4 provides steps for accessing the IDC library on the worldwide web.

Chapter 2. Influenza Outbreaks and its Social Impact

2. Introduction

This section discusses the global dilemma of influenza and fundamental background information pertaining to early detection of influenza, both of which are the focus of this Interdisciplinary Qualifying Project (IQP). In order to properly and effectively combat the threat of influenza, it is necessary to understand the history of influenza and what strain caused each major pandemic. This understanding shows the incredible damage that influenza is capable of, as well as hard evidence that scientifically analyzing and researching influenza will continue to allow humanity to effectively combat the virus. Furthermore, it is highly beneficial to review how influenza spreads from host-to-host in order to develop effective preventive measures to limit the possible spread of influenza. Although effective preventative measures are currently deployed, humans are still susceptible to the influenza virus. For that reason, state-of-the-art diagnosis and treatment options to contain the spread of the virus must be leveraged. The ability to correctly diagnose influenza before the individual becomes infectious also medical professionals to take appropriate action and limit the spread of influenza in the population. This chapter presents some of the methods that are used to diagnosis influenza and compares their effectiveness. Some of these methods allow for the early detection of influenza which in turn can be used to preemptively isolate or treat individuals. Finally, this chapter reviews the material properties of several substances in order to determine what role the surrounding environment has on the spread of influenza. Understanding the historical effect, the modes of transmission, prevention and diagnosis, and treatment options for influenza enables the discussion of proper containment procedures and public health measures.

2.1 Influenza as a Historical and Global Challenge

Influenza is believed to have its origins in the ancient civilizations of Greece and Egypt. Hippocrates records a disease displaying influenza like symptoms in *The Book of Epidemics*, in 412 BC. Homer's *The Iliad,* also records a disease that spread through animals and people alike. These records however, do not mention coughing as a symptom of the rapidly spreading disease, casting doubt on whether this disease could actually be influenza. Medical records of ancient times did not specifically identify the cause of the outbreaks as influenza. During 1918 Spanish flu, the medical community began taking far more detailed records of influenza outbreaks allowing for closer and more accurate analysis. The records confirmed a classification of cyclical infectious outbreaks.

2.1.1 Historical Impact of Influenza

The first outbreak clearly recorded was an epidemic that affected Europe from 1173 to 1174. Other data collected by Fujikawa, an early Japanese physician and historian, indicated 46 separate epidemics in Japan from 1862 to 1868 (Kentaro, 1997). Another notable European outbreak occurred in 1510 (Potter, 2001). The disease was described as a "gasping oppression" with coughing and fever as other symptoms (Potter, 2001). The first recorded influenza pandemic occurred in 1729 and started in China, spread to Russia, and then spread to the continent of Europe within 6 months. Another pandemic was recorded between the years of 1781 and 1782, where a strain was discovered in China and then spread to South Asia (Potter, 2001). The first recorded influenza pandemic occurred in 1729 and it started in China, spread to Russia, and then to the continent of Europe within 6 months. Another pandemic was recorded between the years of 1781 and 1782, where a strain was discovered in China and then spread to South Asia (Potter, 2001). As shown in Figure 1, influenza spread through Thailand and Vietnam to the

Philippines and Indonesia, reached to India and other countries around the Bay of Bengal (Potter, 2001).

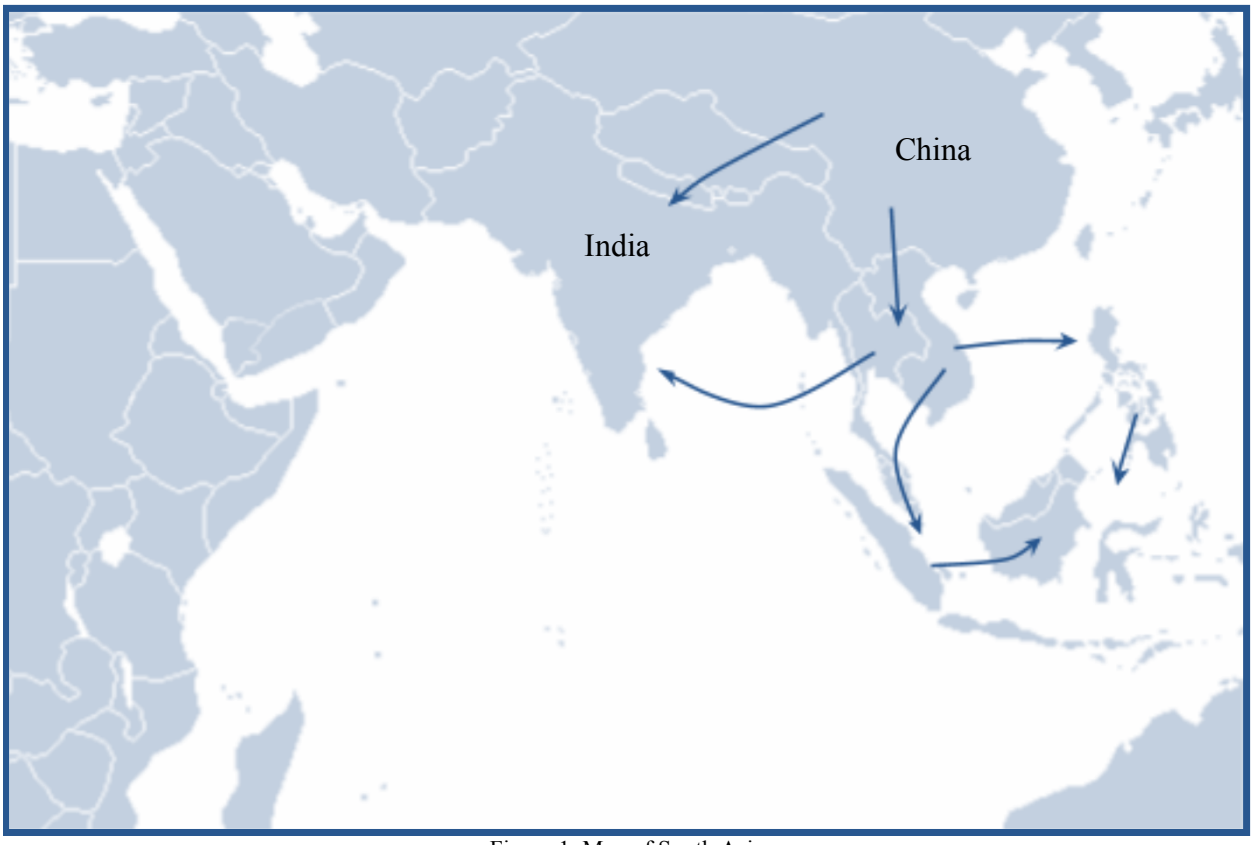


Figure 1. Map of South Asia

1918 Spanish Flu - The Spanish Flu of 1918 known at the time as influenza (BMJ, 1918, JAMA 1918), identified today to be the H1N1 influenza strain), was the largest and deadliest influenza pandemic in human history. It was estimated that over 500 million people were infected and around 50 million died from influenza-related complications (Billings, 2005). More deaths resulted from the 1918 Spanish flu than all the deaths from World War I. Furthermore, the total number of deaths was comparable to the deaths from World War II and other military conflicts in the 20th century (Taubenberger , 2006). The historical records of the 1918 Spanish flu were considered to be more informative than earlier influenza data. In the earlier influenza pandemics, there were limited hospitals to provide treatment and many infected individuals were

treated in their homes. During the 1918 Spanish flu there were more centralized treatment centers and hospitals to provide care to infected individuals (Billings, 1997). An overview of the historical data collected by the Chicago American Medical Association showed the deaths per 1000 people vs time during the Spanish flu pandemic (Billings 1997, Sealey 2010, Taubenberger 2006). Figure 2 shows the plots of the data of the 1918 Spanish flu.

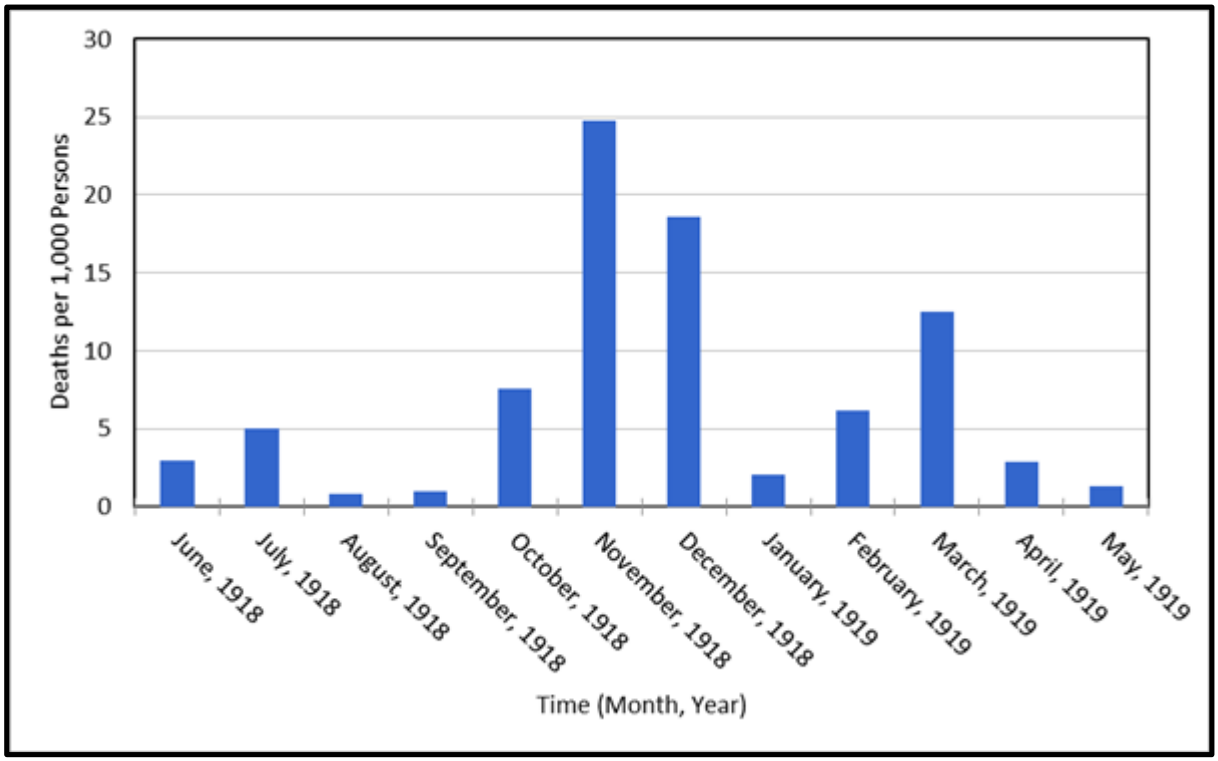


Figure 2. 1918 Spanish flu: Proportion of Death vs. Time

In this figure, there were three distinct waves of deaths from 1918 to 1919. The first and smallest wave of deaths was followed by extremely deadly waves. During the deadliest wave, there were 25 deaths per 1000 persons, an extremely high number that rivals all other pandemics (Morens et al., 2006). Different strains of influenza continued to appear worldwide. Influenza strains first appeared in the United States in the early part of 1918. The research work conducted by Morens et al., 2006 and the references cited in their paper suggested that the influenza virus was originally transmitted from birds to humans in the period of 1915 - 1918. The exact origin of

the pandemic strain was still unknown. There was a general believe that the virus was first transmitted to humans and farm animals in France (Connor et al., 2000). From France, it spread to nearby European countries and then spread to the United States, Africa, Russia and China (Cooner et al., 2000). The spread of the 1918 Spanish flu is shown in Figure 3 (Garrett, 2016).

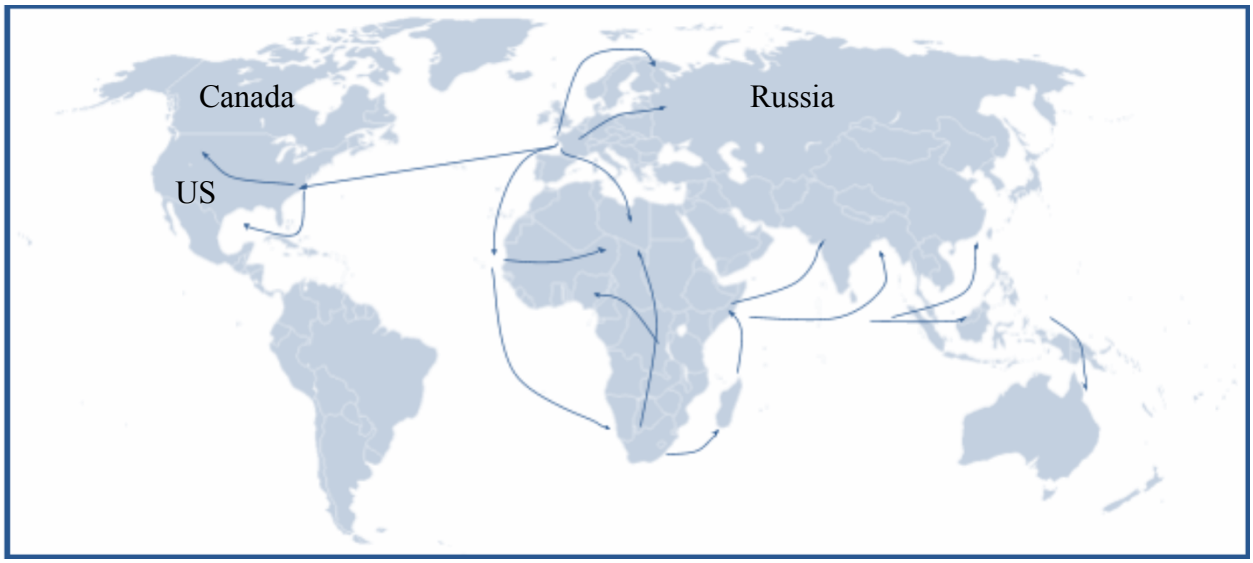


Figure 3. Spread of the Spanish flu in 1918

During this time, the virus underwent a significant antigenic shift that created a novel strain to which humans and swine were both naive (Morens et al., 2006). The overcrowded military camps of World War and limited access to public health facilities accelerated the transmission of the disease from person to person. Lack of knowledge about influenza at the time and the failure to stop infected individuals from travelling were catalysts for the rapid spread of the disease to many parts of the world, including remote Pacific Islands and Antarctica (Morens et al., 2006).

The 1918 strain is known today as the most aggressive influenza strain. Infected individuals with this strain may suffer from pain, headache, fever, chills, cough, nausea and many other influenza type illnesses. It infected many people worldwide and was responsible for

mortality rates of influenza infections (Morens et al., 2006). Unlike traditional influenza strains, this particular variant targeted young adults, the elderly and others with weak immune system, Figure 4 (Taubenberger, 2006; Sealey, 2010; Viboud, 2012) shows plots of the number of deaths vs the age of the patient.

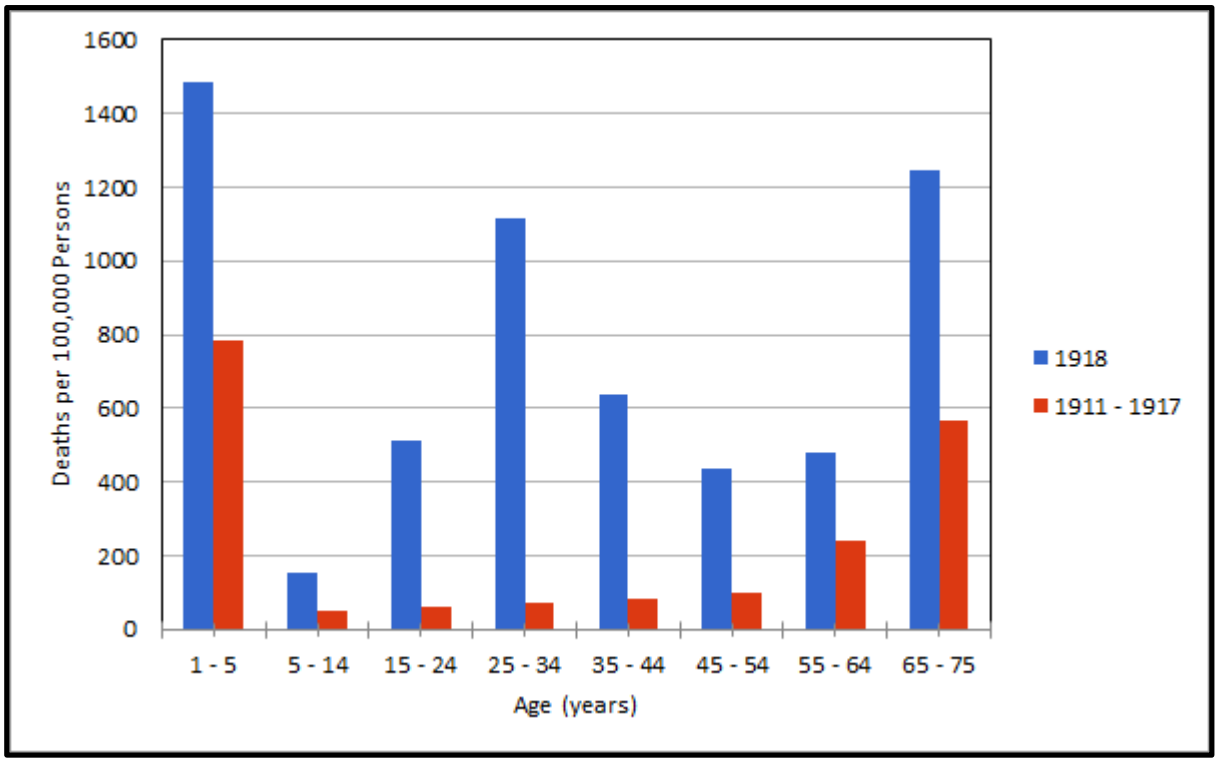


Figure 4. 1918 Spanish flu Number of Deaths vs Age

This abnormality could had been attributed to the war, exposure of individuals with weak immune systems or that there were antibody-dependent infection factors (Morens, 2006). Further factors which contributed to high mortality rates from the outbreak included the lack of trained medical professionals, limited preventative supplies, and the inability of the healthcare to handle the volume of corpses (Billings, 2005). Other oddities of the 1918 influenza strain included the fact that it infected both humans and swine simultaneously (Morens, 2006). All influenza type A strains circulating in humans as of 2006, with the exception of H5N1 and H7N7 avian strains, can all be traced back as variants of the 1918, H1N1 strain. This H1N1 strain is thought to be the

ancestor of all known human and swine H1N1, H2N2 and H3N2 strains. None of these subsequent strains have proved to be nearly as deadly as the 1918 HINI Spanish flu. It is unknown what caused the 1918 pandemic to have such high mortality rates. The lack of knowledge about influenza infections, inability to restrict travel, and unique autoimmune response caused by the virus all contributed to the high mortality rates. The influenza fatality rates were greater than 2.5% and this was considerably higher than 0.1% of other influenza pandemics (Billings, 2005). This particular outbreak was considered to be the deadliest of the 20th Century and ushered in a new age of medical practices. Public health measures were developed, genetic research on influenza began, and the severity of a deadly outbreak was realized.

1957 Asian Flu - The 1957 Asian flu pandemic started in February of 1957. Like most widespread influenza infections before it, the most notable exception being the 1918 Spanish flu, the strain emerged in Asia and spread to the rest of the world (Jackson, 2009). The map shown in Figure 5 displays how the Asian flu spread from China to other countries around the world (Garrett, 2016).

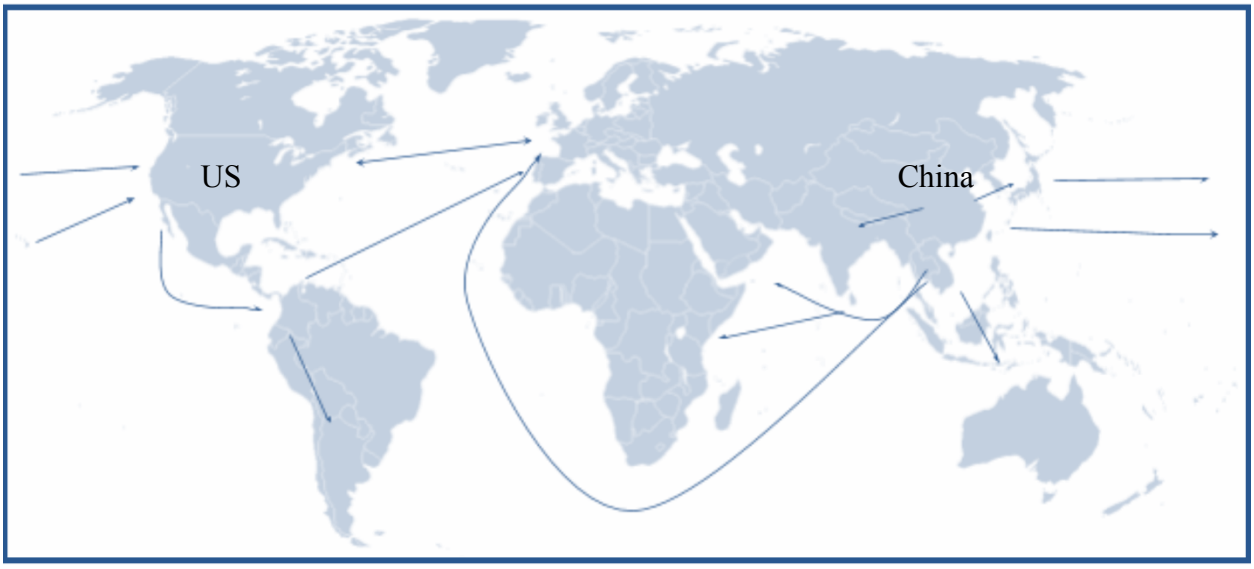


Figure 5. Spread of the Asian flu in 1957

As one can see, influenza spread both east and west to the Middle East, India and North America. From there, the 1957 strain spread to Europe and South America. The worst hit countries were Panama, Chile, Mexico and Hungary; each experienced significant population infections (Viboud et al., 2016). Other countries that were heavily affected by influenza were Taiwan and India which suffered 10,000 cases and 1,000,000 cases respectively. By the summer of 1957, the pandemic reached the United States and caused an estimated deaths of 116,000 (Kilbourne et al., 2006). By early 1958, it was estimated that over 9 million people in Great Britain had been infected and about 14,000 people died from secondary complications. Although this outbreak was contained, there was a slight increase in the influenza-related deaths in January of 1958. It was not known if this was a second minor wave or a result of the pandemic itself (Jackson et al., 2009). The Asian flu had a documented death rate of 0.13%, which was further complicated by improper use of antibiotics. This was used to treat secondary infections and other infections that attack individuals with weak immune system. Many healthcare providers were also infected (Viboud et al., 2016). It was estimated that 1.1 million people died during this

pandemic (Henderson et al., 2013). The Asian flu viral strain, referred to as the H2N2, was later determined to be the directed descendant of the 1918 H1N1 virus. However, the viral mutations led to the conclusions that the H2N2 virus was far less fatal than its predecessor (Kilbourne et al., 2006). Given the strain's less lethal nature, this outbreak provided scientists the opportunity to observe the role of vaccinations against influenza and post-pandemic effects. The 1957 Asian flu was the first influenza pandemic where vaccination was used to reduce the rapid spread of influenza. However, since the production of the influenza vaccination was limited, doctors, nurses, and other medical professionals who were in direct contact with infected patients were given priority (Henderson et al., 2013). It circulated in humans for 11 years until it was replaced by the 1968 H3N2 Hong Kong virus.

1968 Hong Kong Flu - The Hong Kong Flu virus, known scientifically as the H3N2 virus, started in the Hong Kong region of Southeast Asia and spread around the world rather quickly (Viboud, 2005). The global spread of the 1968 Hong Kong flu virus is illustrated in Figure 6.

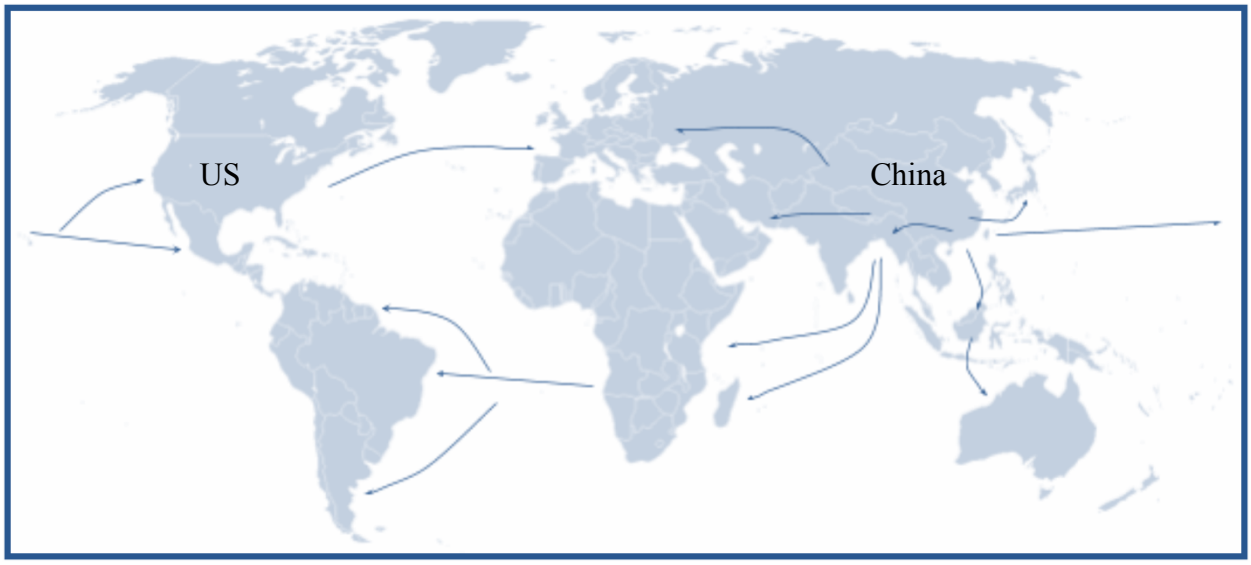


Figure 6. Spread of the Hong Kong flu in 1968

This variant caused unusually high death rates in the United States and Europe. It was noted by scientists that the similarity between the N2 variants of the H2N2 and H3N2 virus allowed regions of the world hit particularly hard by the 1957 Asian Flu variant to suffer less from the 1968 strain. Although the same H3N2 virus did return in following years, there were mercifully few deaths. An estimated 33,800 people died worldwide, making it the least deadly pandemic of the 20th Century (Viboud et al., 2005).

The H3N2 virus was an antigenic shift variant of the H2N2 virus that affected many people worldwide (Pike, 2011). It was suggested that the H3N2 virus entered a host species, commonly swine or birds, and then underwent large enough genetic mutations which was no longer the same virus. This allowed the virus to re-enter human circulation without encountering individuals who had antibodies against the previous virus variant. The lower rate of death was a result of the vastly improved medical care and public health measures (Viboud et al., 2005). Other factors included possible immunity from the 1957 virus strain, improved medical care and public health and the availability of antibiotics, which helped limit the effects of secondary complications (Viboud, 2005).

1977 Russian Flu - A mild outbreak of influenza started in Asia during the summer of 1977. It became known as the Russian flu, or the Red flu, due to its large impact in the Soviet Union. By some accounts, the virus actually surfaced in May of that same year in Northern China (Kilbourne, 2006). The spread of the 1977 Russian flu is shown in Figure 7.

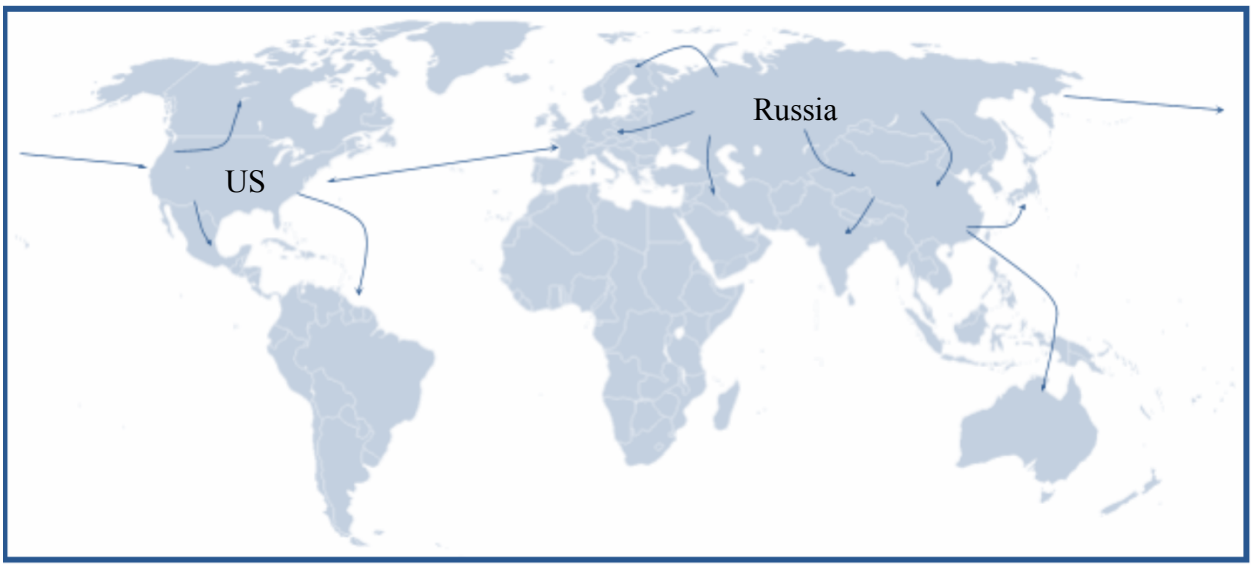


Figure 7. Spread of the Russian flu in 1977

From Russia, the virus spread to China and Europe as well as to the United States. By 1978, the virus had spread around the world. Outbreaks in American schools and military camps were reported. There was a noticeable outbreak at the U.S. Air Force Academy in Colorado where 76% of the cadets were infected. There were no records of died cadets from this outbreak (Rozo, 2015). The virus was very similar to the 1957 pandemic strain of the Asian flu and was identified as a re-emergence of the H1N1 strain (Kilbourne, 2006). Figure 8 shows a virus genetic chart of influenza strains.

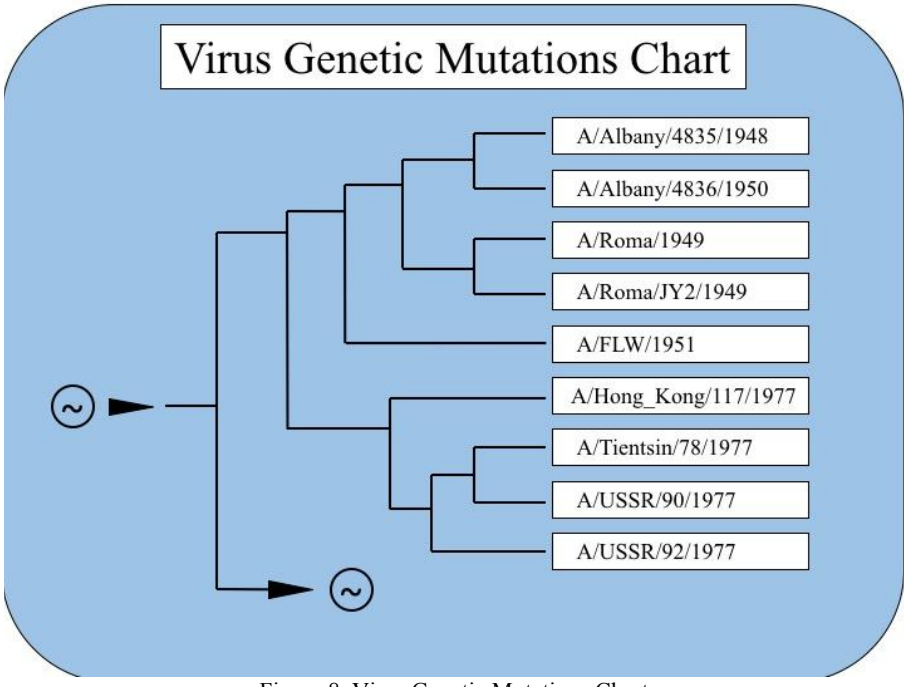


Figure 8. Virus Genetic Mutations Chart

The Russian or Red flu strains were considered as direct descendants of the 1968 Hong Kong influenza strain. This virus was 98.4% identical to the strains in 1957 Asian flu with only four amino acid differences (Rozo, 2015).

2009 Swine Flu - The 2009 Swine flu was a variant of the H1N1 virus, now classified as the H1N1 pdm09 virus. It was first recorded in April, 2009 in the United States and States such as Alaska, Connecticut, Delaware, Hawaii, Illinois, Massachusetts, Texas, Utah, Wisconsin, and Wyoming had many cases of influenza flu illnesses. In the United States, the 2009 Swine Flu mainly spread among summer camps as well as later when school started. This second wave infected more individuals than the first wave (Jhung, 2011). The map in Figure 9 depicts the relative spread of the 2009 Swine Flu (Pawaiya, 2009).

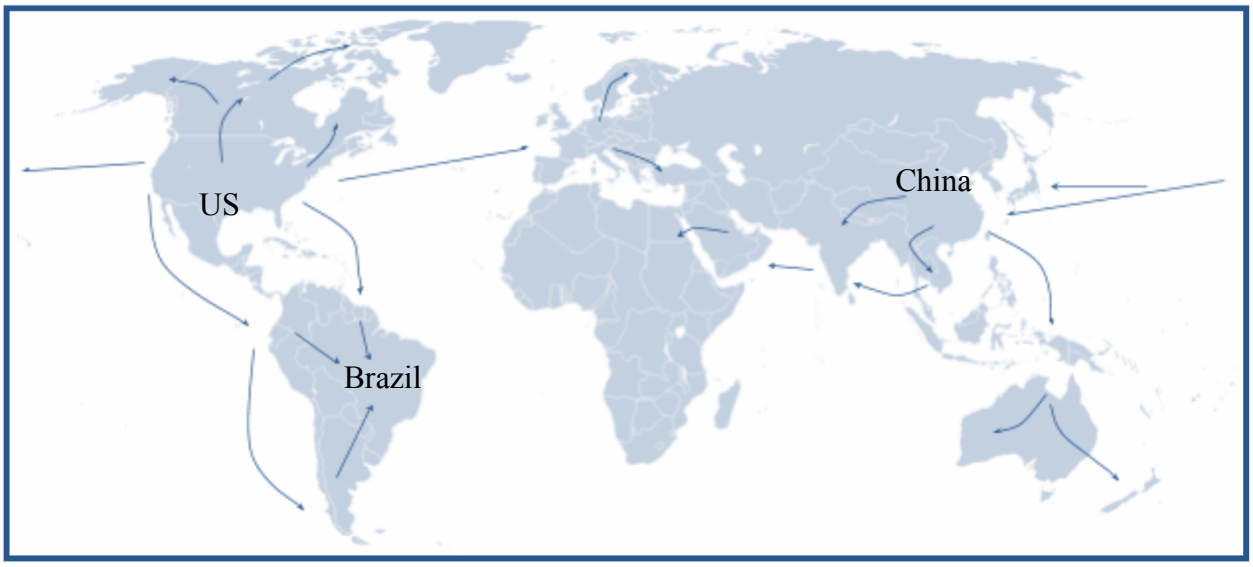


Figure 9. Spread of the H1N1pdm09 Virus Strain in 2009

The 2009 Swine Flu also spread to Asia, South America and Australia. However, it produced a limited number of deaths in one month and 429 influenza cases were reported. The strain was determined to be compose of the American Swine H1N1 Lineage and the European Swine H1N1 Lineage (Jhung, 2011). Fortunately, public health procedures limited the total number of deaths and by May 2010, the virus was in decline (Jhung, 2011). In August of 2009, 477 deaths were reported in the United States. Of those 477 deaths, 36 were children under the age of 18. It was also noted that of these 36 children, 64% had other underlying, critical medical conditions which could have contributed to their deaths. This strain largely targeted children and the elderly with 13% of deaths of people over the age of 65, compared to the more typical 90% (Viboud, 2016). Worldwide it was estimated that approximately 150,000 people died from the virus. Increased media coverage, better treatment plans, and improved medical care proved to be effective in the effort to combat the flu related illness (Viboud, 2016).

2.1.2 Seasonal Influenza

The defined seasonal periods of influenza epidemics have historically been explained by the cold and dry climate regions. This has since been challenged, with studies now showing that tropic zones also have well defined months that have an unexplained increase in influenza cases (Tamerius et al., 2012). In the United States, the flu season can start as early as October and last until May (CDC, 2017). While influenza seasons in regions across the world remain constant and defined, no reasonable explanation for these occurring patterns of influenza has been identified (Tamerius et al., 2012). The overall percent of deaths resulting from pneumonia and influenza, collected and recorded data by the CDC are plotted in Figure 10.

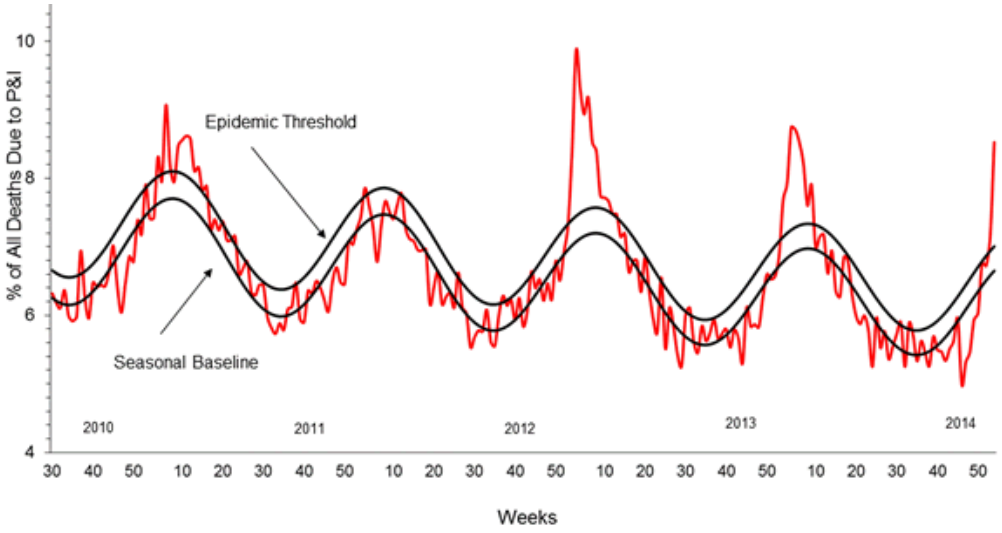


Figure 10. Pneumonia and Influenza Mortality

There are continued efforts to understand the mechanisms that promote influenza seasonality. A number of factors have been suggested to be responsible for the occurrence of seasonal influenza. Biological causes of influenza seasonality are largely attributed to viral evolution. Mutation of viral antigenic epitopes especially in influenza A have been recorded to undergo frequent mutations (Lofgren, 2007). These mutations allow the novel viral epitopes to be unrecognizable by host immunoglobulins. As the host immune system is unable to identify

the novel viral pathogen, the virus is able to infect the host uninhibited. The host immune system is capable of eventually identifying and targeting the virus. This allows the strain to then become resistant to the influenza strain. Viral evolution and host adaptation are noted to generate cyclical patterns, responding to one another in a pattern that closely resembles the observed seasons of influenza (Lofgren, 2007).

A second potential contribution to seasonal influenza was suggested to be a result of seasonal host health conditions. Observations have been made that alterations in melatonin secretion mediated by the annual light/dark cycle have the potential to leave individuals predisposed to infectious disease (Dowell, 2001). The third predicted mechanism of influenza seasonality was regarded as changing host behavior. This prediction relies on the association of increased time spent indoors during winter months and long periods of mass gathering in the workplace and school during the epidemic disease seasons (Lipsitch, 2009). Populations of individuals spending more time in confined indoor locations created high risk for transmission of influenza form person to person.

2.1.3 Continued Threats of Influenza

There are significant concerns regarding the H5N1 strain of influenza. This particular strain is known to currently reside in birds, but does occasionally infect humans. While this strain has a devastating 40-60% mortality rate in humans, it rarely transmits to humans. Humans can be infected through close contact with H5N1-infected birds, but it does not seem to be transmitted through food as indicated in the publication by the World Health Organization (WHO, 2017). The danger of H5N1 influenza comes from its extremely high mortality rate and the relatively few genetic shifts required for human to human transmission. Experiments were conducted in controlled laboratory environments by scientists to better understand the H5N1 variant and its modes of transmission from human to human (Viboud, 2016). Severe

complications of H5N1 are difficulty breathing, pneumonia and seizures, and all of which can lead to death (WHO, 2017). Given that H5N1 variant has a documented death rate of over 40% and the fact that the 1918 Spanish Flu - the deadliest influenza strain in human history, had a death rate of 2.5%, it is possible that an outbreak of H5N1 could potentially cause far more deaths than the 50 million deaths in 1918 (WHO, 2017).

2.2 Influenza Modes of Transmission

Influenza has several modes of transmission that include: direct contact, indirect contact and non-contact (see Figure 11; Otter, 2016).

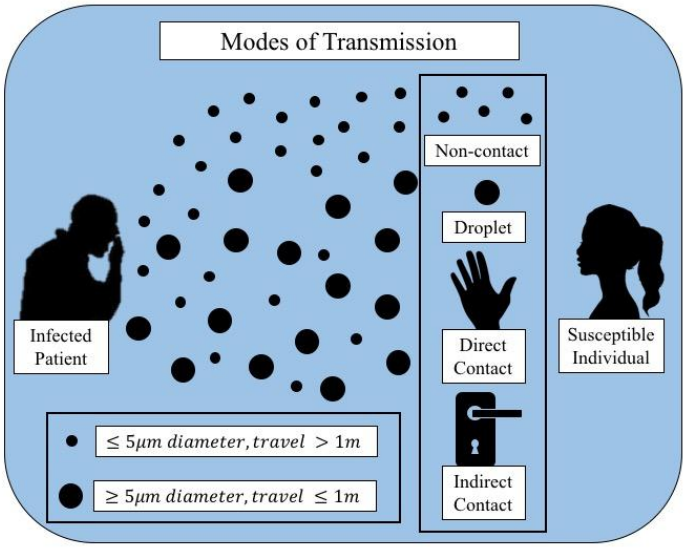


Figure 11. Transmission Modes

Direct contact is characterized as contact between bodily fluids such as large respiratory droplets, mucus, or breaks in the skins. Indirect contact includes transfer of the infectious agent to a contaminated object, through which a susceptible host then is infected. Non-contact is defined as airborne or droplet transmission where airborne infectious agents are exhaled by a host and then inhaled by a susceptible host (CDC "How", 2016). A visual diagram of all three modes of influenza transmission is shown in (Figure 12; McGraw-Hill).

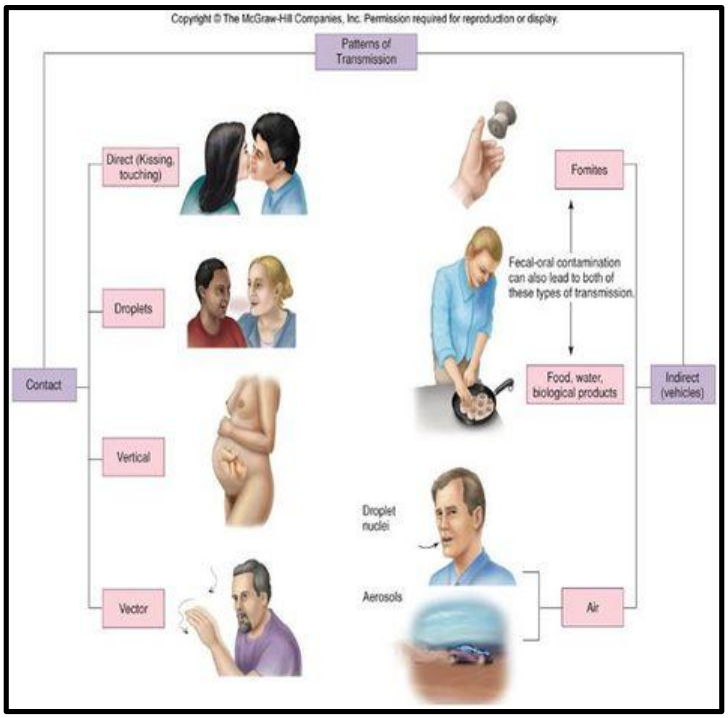


Figure 12. Influenza Direct and Indirect Contact Transmission

Direct and indirect contact encompass several different modes of transmission. In order to learn how to combat and effectively prevent the spread of influenza it is vital to understand how influenza is transmitted between hosts.

2.2.1 Direct Contact

Direct contact occurs when viral strains are passed directly from one host to another. This mode of transmission is one of the least effective ways of transmitting the virus (Mubareka et al., 2009). This can be attributed to the intolerable conditions that the skin presents to the virus (Weinstein et al., 2003). Furthermore, an overlap of transmission methods often occurs, which makes identifying a single mode of transmission difficult (Mubareka et al., 2009).

Figure 13. Direct Contact: Skin-to-Skin Transmission

Direct contact occurs when influenza droplets invades the respiratory system of a susceptible host. This most commonly occurs when the infected host releases these droplets directly to another person. Common examples include coughing and sneezing; these can cause the virus to immediately enter the respiratory system (Weinstein et al., 2003). Droplets can also land onto the hands of the susceptible host from which the virus travels to the host's face. The virus can also be transmitted through direct skin-to-skin contact which includes hand-shaking and other physical contact as shown in Figure 13. The transfer of bodily fluids from person to person can also be considered as direct contact and can transmit the virus (Mubareka et al., 2009). As direct contact covers many of the day-to-day interactions of humans, it is one of the most common modes of transmission. Therefore, it is necessary to be aware of the modes of influenza transmission so that effective preventive measures are taken.

2.2.2 Indirect Contact

The significance of indirect contact transmission is controlled by the relative environment in a particular area. It has been shown that the influenza virus can survive on several surfaces in environments where humidity is between 35% - 49% and has a temperature of 28°C (Weinstein et al., 2003). Under those conditions, viral strains can survive up to 48 hours after contact, 12 hours from porous surfaces, and up to 5 minutes after contact with skin. Furthermore, the virus is capable of moving from various surfaces to hands for up to 24 hours after contact with nonporous surfaces and 15 minutes after contact with porous surfaces (Weinstein et al., 2003). Indirect contact enables influenza to enter new hosts even if they had not contacted infected individuals. Examples of this transmission process begin with contagious individuals who touch surfaces such as door knobs and tables. If a healthy individual subsequently were to touch those surfaces, aerosol droplets could be absorbed into mucus membranes and into the body. Nosocomial modes of influenza infection transmission are included in Figure 15 ("Contact", Bode Science, 2017). They reveal how the indirect contact can be conducted from a number of surfaces found in health care settings. As indicated in the image, it becomes easy to understand how quickly a healthcare provider could unintentionally contaminate these surfaces while administering patient care. Understanding the ability to become infected by influenza through this mode of transmission makes the provisions utilized to control this mode all the more pertinent.

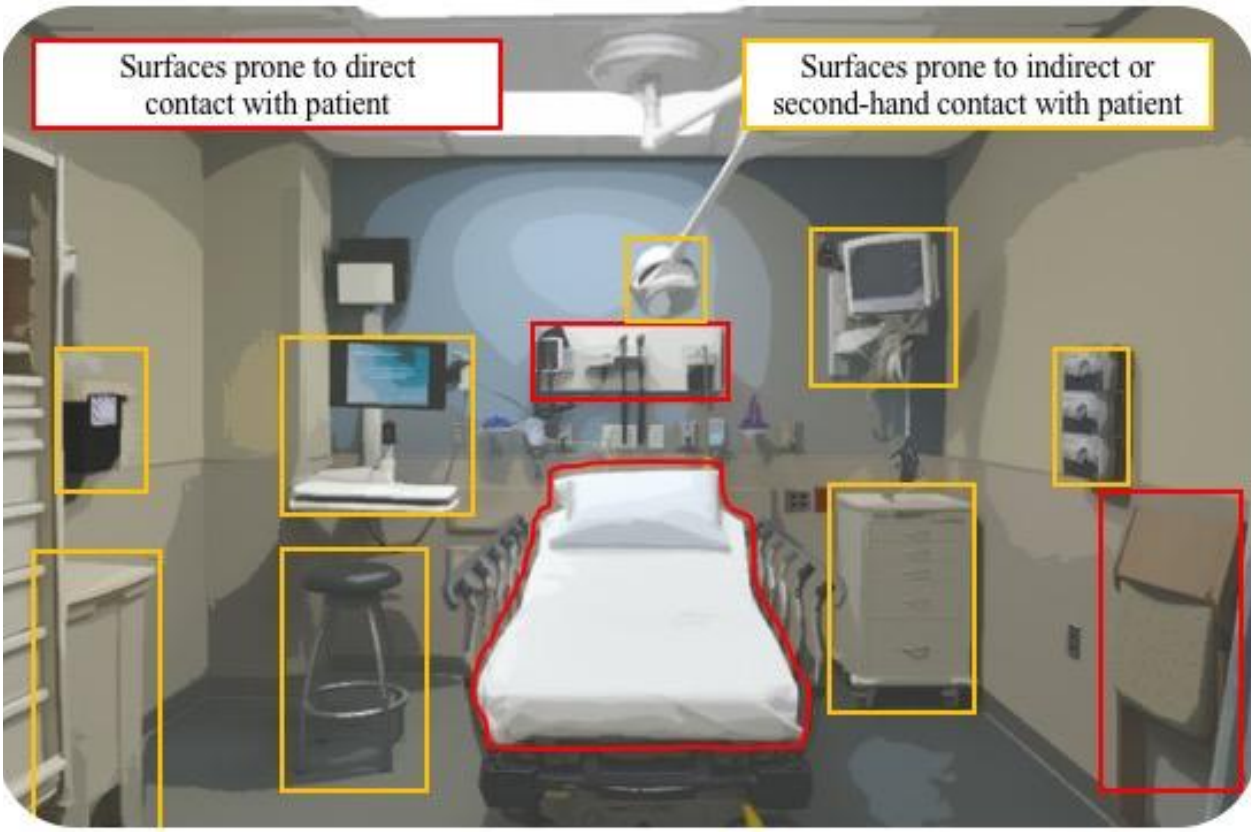


Figure 14. Hospital Based Surfaces for Infection

Figure 14 provides examples and reveals how awareness of this mode of indirect transmission is being addressed by the CDC. It is useful to inform the population about surfaces which can host influenza virus for long periods of time. Additionally, it presents techniques to clean and sanitize these surfaces to reduce the transmission of influenza. Distribution of these informational posters are typically present in health care centers in addition to public facilities. These can specifically include bathrooms and other areas where it is useful to remind people of proper sanitation and awareness can help reduce transmission of Influenza.

Figure 15. Potential for Indirect Contact

Indirect contact relies on a surface to travel. Transmission occurs commonly through objects that humans constantly pick up and use. Examples of such objects include food, computers, and phones. For this reason, surfaces shared between multiple humans may increase the exposure to possible hosts. Surfaces include door handles, tables, and silverware.

Figure 16. Frequently Touched Surface

Notably the majority of influenza transmission has been identified within locations such as homes, schools, and workplaces (Greatorex, 2011). It is assumed that fomite transmission via this indirect contact is conducted by individuals touching communal items and surfaces. Research has revealed that fomites (transmissible infectious viral agents) are capable of being detected on surfaces up to 24 hours after initial application via RT-PCR (Greatorex, 2011). However, UK Health Protection Agency research indicates viral viability (ability to cause infection) sharply decreases after 4-9 hours from initial application. Fomite reservoirs have been identified on a number of household and clinical items. Metal surfaces in particular have been of particular interest due to specific metals demonstrating the ability to reduce transmission of bacterial pathogens in healthcare settings (Noyce, 2006). Among these metals of interest, Copper has demonstrated unique antiviral properties that promote rapid viral inactivation within 6 hours of surface contact (Noyce, 2006). Although the mechanisms of this metal surface and viral interaction are not fully understood, it was predicted based on previous findings that copper facilitates disordering of single-stranded nucleotide sequences (Rifkind, 1976). This crossing linkage was suggested to result in the viral genome degradation and subsequent loss of viral

viability on the copper surface. Conversely, metals such as stainless steel have been revealed to be capable of harboring viable viral strains for at least 7 days through a number of environmental conditions (Perry, 2016). Infection via these indirect transmission vectors is ultimately mediated by the fomites being transferred to individuals. Surface-to-human transmission is therefore facilitated by fomite transmission to surfaces such as an individual's fingers. Studies have indicated that the influenza virus can survive on skin surfaces and remain infectious for up to 30 minutes (Thomas, 2014). Understanding the presence of viral fomites on various surfaces and the timeframe of viral viability on these surfaces support the efficacy for improved initiatives promoting improved hygiene in combating influenza.

2.2.3 Noncontact and Airborne Transmission

Aerosol agents are the primary means of transmitting influenza A strains. Studies have shown that approximately half of all infections occur through these means (Cowling et al., 2013). Aerosol droplets are commonly defined as spherical liquid droplets that are less than 5μm in diameter. These particles are suspended in air and remained airborne for extended periods of time. A 5μm droplet takes 62 minutes to settle to the ground and droplets of less than 3μm do not settle on the ground. Particles are small enough to be inhaled and deposited in the lower respiratory tract (Tellier et al., 2006). Influenza, as described, utilizes all three modes of transmission when transmitting to a group of new hosts. Historically, influenza has an extremely high rate of infection and is capable of infecting a large number of individuals in close proximity to each other (Rothberg et al., 2015).

Figure 17. Surfaces Which Influenza May Survive On

Despite being far less effective in colder temperatures, this combination of survivability allows influenza to survive and spread in practically all environments (CDC "How", 2017). Influenza not only could be spread by a clearly sick patient, but also by an exposed individual before they begin to exhibit any symptoms (CDC "How", 2017).

2.3. Preventive Measures

The complete prevention of influenza cannot be guaranteed, however there are public health steps one may take in order to stop the spread of the virus. These may have the purpose of either directly protecting the population from influenza or of halting the spread of the disease from one person to another. Vaccinations helps to increase individuals' resistance to the flu, while basic hygiene and cleanliness help to prevent the spread of the virus. Since the majority of the methods of prevention require the general population to take action individually, the best

method to increase prevention is public outreach. Awareness of available vaccination centers, public health communications, diagnostic centers and treatment options play major roles in flu prevention. Reminders to get vaccinated, information on good preventative hygiene, lists of symptoms to watch for and information on what to do should someone get sick, should be available to the public to encourage effective preventative behaviors. The intent of this section is to evaluate and analyze past preventative measures.

2.3.1. Public Health

Awareness - The ability to educate and inform the public is essential in public health and preventing the overall spread of the flu. This challenge is accomplished at the macro level, with large organizations and government taking the lead on promoting awareness. For instance, the Center for Disease Control (CDC) is the premier Government Agency in the United States for health promotion, prevention and preparedness. In particular, they have dedicated extensive resources towards understanding, promoting and combating the threat of influenza for years. As a result, CDC data collections and recommendations are considered the benchmark for combating influenza.

Environment- One potential way to decrease the likelihood of contracting influenza may be to stay in a warm and humid environment. A study by the Public Library of Science Pathogens from 2007 used guinea pigs to test the spread of influenza in varying temperatures and humidity. The study found that influenza had a greater rate of transmission in low humidity (relative humidity of about 20% to 35%) and in lower temperatures of about 5° C (Lowen et al. 2007). At high humidity and temperature (relative humidity on 80% and temperature of 20°C), virus transmission did not occur. This study correlates transmission patterns of influenza to

climate, however almost everywhere in the world experiences seasonal flu. This suggests that an individual cannot fully protect themselves by means of climate alone.

Hygiene/Sanitation- The simplest method for preventing the spread of influenza is keeping good hygiene and cleanliness. This practice is also used in reducing cases of more major diseases such as cholera and dysentery in the 1930's and 1950's(CDC "Achievements," 1999). During this time, health departments were founded and provided information on hygiene to the public, which played a major part in disease reduction (CDC "Achievements," 1999).

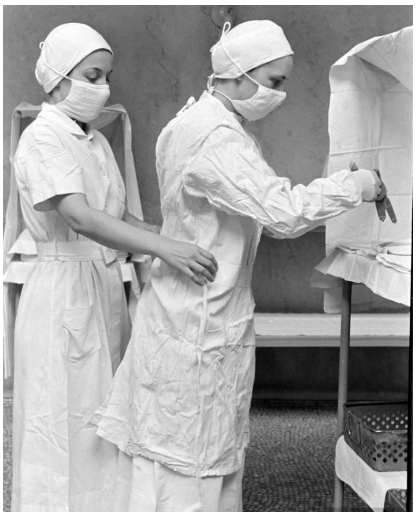


Figure 18. Vintage Healthcare Provider Protection

An increase in hygiene helps to prevent contact with people who are infected with the flu, in addition to promoting self-isolation if sick. This prevents the spread of influenza through direct contact and airborne routes. Avoiding touching the eyes, mouth and nose, disinfecting regularly used surfaces, and hand washing may all prevent contracting influenza through indirect contact (CDC "Everyday", 2017). Should a person contract influenza, the CDC recommends isolating oneself until at least 24 hours after the fever subsides naturally (CDC "Everyday", 2017). In addition to self-quarantining, the CDC recommends good sickness habits, such as coughing and sneezing into a tissue to be discarded, avoiding close contact with uninfected people and washing hands regularly.

2.3.2. Vaccination

Vaccination is recommended by the CDC as the best way to prevent influenza, reducing the chances of contracting the disease by 40 to 60 percent (Treanor et al., 2012). A number of vaccination centers are available across the United States. Vaccination is also shown to sometimes decrease the severity of the flu, thus resulting in less time being spent in the hospital, in cases where hospitalization is required (Arriola et al., 2017). Receiving the vaccine for the flu is critical for "high risk" demographics, which include the elderly, young children and people with chronic illnesses, as well as, anyone who may be in contact with the aforementioned individuals. For this reason, the annual flu vaccine is made readily available, and about 149.5 million doses are distributed in 2016-2017 season as shown in Figure 19 (CDC "Historical" 2017) and an estimated 151 to 166 million doses to be made available for the 2017-2018 season (CDC "Historical" 2017). These doses may be given to the public at their primary care physician's office, local hospital, urgent care facilities, pharmacy clinics, or, in the case of college students, campus health services. To maximize effectiveness of the vaccine, one should receive the vaccine close to the beginning of one's local flu season, but if that time period is missed, it is better to get it later in the season than not getting vaccinated (CDC, "Key", 2017).

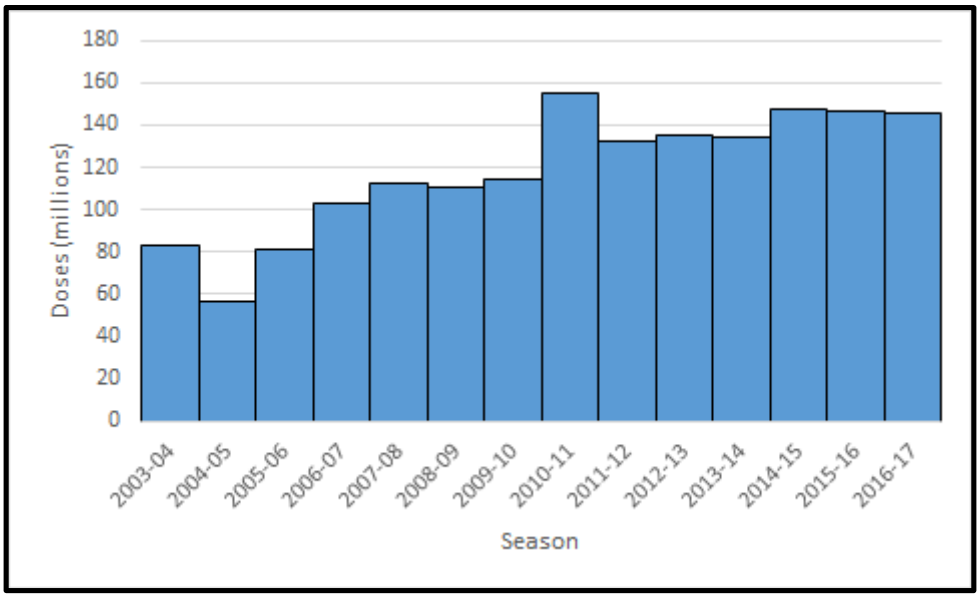


Figure 19. Influenza Vaccine Doses Distributed in the US by Season

The availability of vaccines is only effective if the population is inoculated with them. A series of self-reported surveys estimated that about 45% of people in the United States were vaccinated in the 2015-2016 season (CDC "Flu", 2017). These surveys showed a higher percentage of vaccination in pediatric and geriatric patients, with children 6 months to 17 years of age having an average vaccination percentage of about 59 and people over 65 years of age having one of about 63 (CDC "Flu", 2017). These Figures, acquired from the Behavioral Risk Factor Surveillance System (BRFSS) and National Immunization Surveys (NIS), also have slight differences by gender and ethnicities, including adult women having on average a higher vaccination percentage than men. Overall, coverage does include the "at risk" populations of the old and the young at a higher rate of vaccination.

Vaccination is a process that boosts the body's immune system by introducing a weak or dead version of the virus to the body for the immune system to develop antibodies against and destroy (see Figure 20). This allows the immune system to produce the right antibodies faster

when the full strength virus is introduced into the body. The standard vaccine requires about 6 months to mass produce for public consumption and are therefore planned in February before the autumn flu season. This means that the three or four strains which were predicted and included in the vaccine may periodically be inaccurate, which were seen in a few isolated cases such as the 2014-15 flu season (Zimmerman et al., 2016).

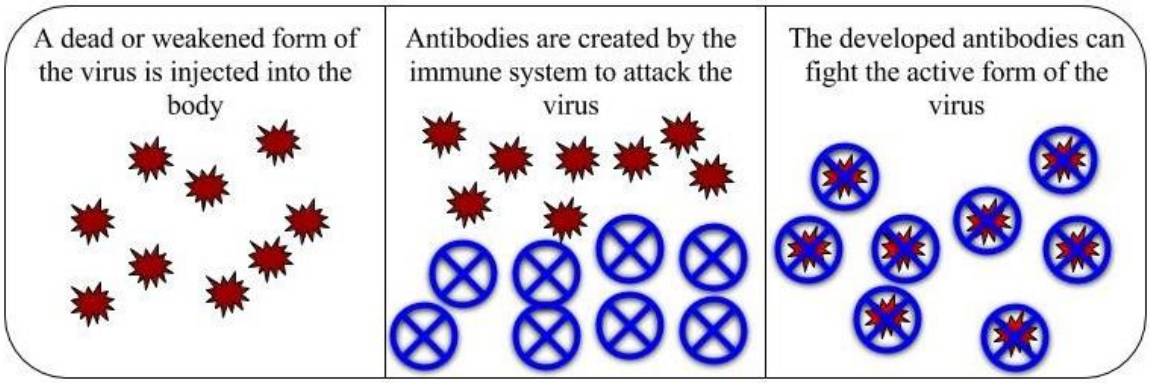


Figure 20. How Vaccines Work

The current method of production of influenza vaccines involves “growing” the virus in chicken eggs. This is more effective for the B strains of the influenza virus than for the A strains, particularly H3N2 (Belongia et al., 2016). H3N2 influenza tends to adapt to its environment and undergoes changes while in the egg (known as “egg-adapted changes”) which result in the vaccine type of the virus being less effective at preventing the circulating type of the virus. A few methods are being attempted to combat this, including growing the virus in mammalian cells (notably “Flucelvax”), combining proteins which trigger immune responses with insect cells (Flublok) and genetically modifying the vaccine strains to be less mutable in eggs. The former two methods, known as cell-based vaccine production and recombinant vaccination respectively, have the added bonus of being quicker to produce than the traditional egg-based vaccines. A

faster production time may allow for a delay of production and a greater likelihood of predicting the correct virus strain.

2.3.3. Patient Placement

There are a variety of options when it comes to patient placement with respect to limiting exposure to infectious diseases. These include single patient rooms, two patient rooms and multi-bed wards. Single patient rooms are preferred when there is a concern over infectious transmission. However, most hospitals and long-term care facilities have multi-bed rooms and must consider competing priorities when determining the appropriate room placement for patients. When there are only a limited number of single-patient rooms, it is important to prioritize them for two independent groups of patients. This includes those who have conditions that facilitate transmission of infectious material to other patients and for those who are at increased risk of acquisition and adverse outcomes resulting from exposure (Siegel et al, 2007). Single-patient rooms are always recommended for patients placed on airborne precautions and are in a protective environment. They are also preferred for patients who require contact or droplet protection (Siegel et al, 2007). Currently, the standard practice as recommended by the CDC is to utilize cohorting, which is defined as "the practice of grouping patients infected or colonized with the same infectious agent together to confine their care to one area and prevent contact with susceptible patients" (Siegel et al, 2007).

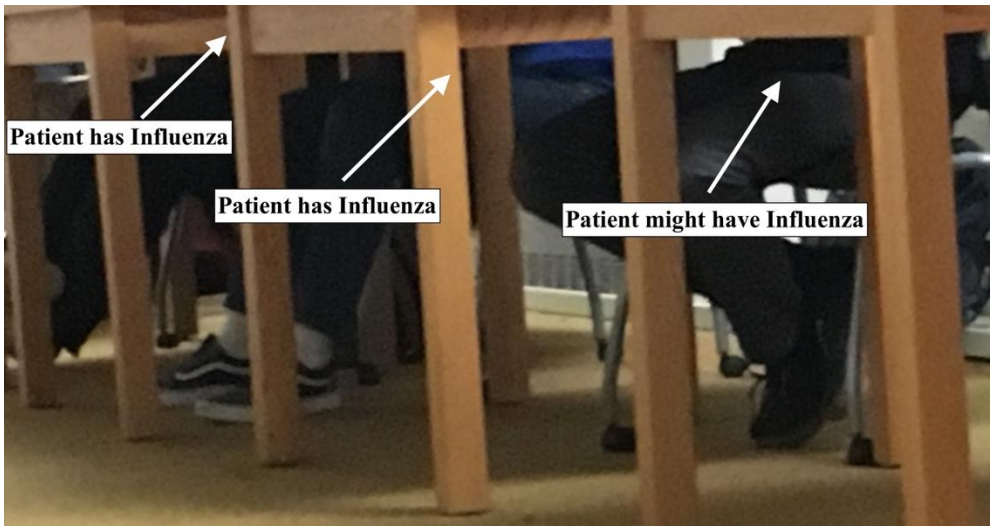


Figure 21. Example of Cohorting

For the purposes of practicality and administration, the current use of cohorting in large hospitals, across the United States, is to group patients presenting with flu-like symptoms in one multi-bed area. This allows for the limited number of single patient rooms to be reserved for individuals who are at a higher risk of receiving infections. The advantage of rapid testing is that a hospital would be able to efficiently place patients in the correct multi-bed ward. The risk of infecting patients who present flu-like symptoms but do not actually have influenza would thus be reduced.

2.4. Diagnosis and Evaluation

Diagnosing influenza cannot be accomplished through symptom presentation alone. As a number of symptoms are shared with other afflictions, as stated above, there is a risk of diagnosing an individual with the flu based off of their clinical manifestation, only to group them with others who are actually infected and in turn infect an otherwise healthy individual. For that reason, laboratory tests were developed in order to positively diagnose patients with influenza and treat them accordingly. Treatment is largely time dependent and focuses on managing the

symptoms of influenza and reducing risk. As a result of the time sensitive nature of the virus' effect on a community, the ability to rapidly detect influenza is invaluable. Diagnosis and evaluation can be divided into three main categories; pre-hospital, clinical, and in-hospital.

2.4.1 Prehospital Evaluation

Prior to patient arrival at the hospital, patients and Emergency Medical Services (EMS) providers can do a simple evaluation to check for the symptoms of influenza. As previously mentioned, the flu is characterized by a rapid onset of symptoms. This can easily be used by patients to determine when they were last feeling well and when they started expressing symptoms. Another easy and inexpensive way for patients to determine if they might have the flu, is to take their own temperature using a home thermometer, in order to determine if they have a fever. Flu fevers usually last 3-4 days, however, according to the CDC, not everyone experiences a fever with the flu (CDC, "Flu Symptoms & Complications", 2016).

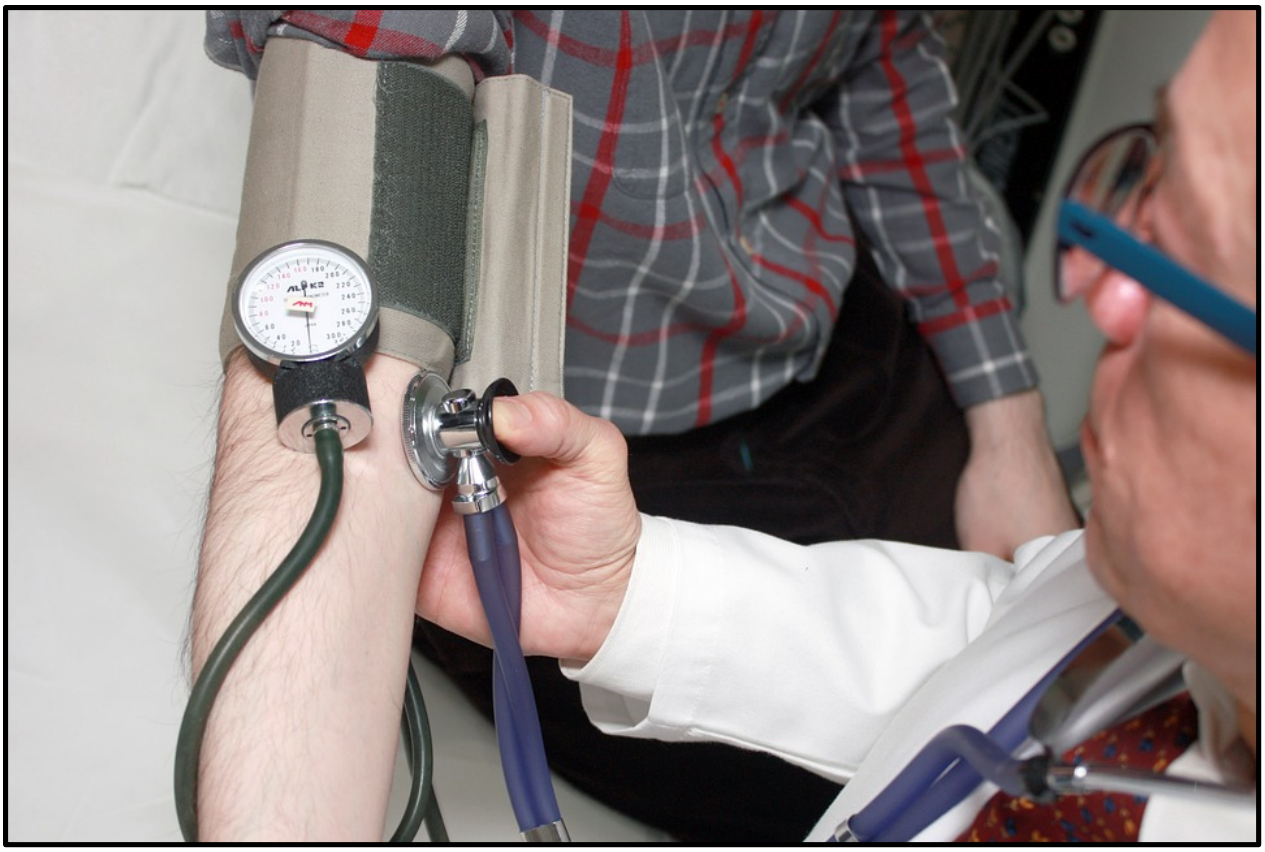


Figure 22. Doctor and Patient

EMS professionals can also use the same guidelines for influenza suspected patients. In the event that EMS professionals are transporting an influenza suspected patient, all staff should be wearing masks and gloves. Lastly, according to the CDC and as previously mentioned, one of the best ways to prevent the spread of the virus is through hand washing, which is something all EMS professionals should do after dealing with an influenza suspected patient.

2.4.2 Clinical Evaluation

The best clinical evaluation techniques rely on the doctors being able to recognize the symptoms of influenza. Disease progression of the influenza viruses of the Orthomyxoviridae family is initiated through virulence factors present in the form of viral proteins (Fukuyama, 2011). Proteins such as hemagglutinin (HA) contribute to pathogenicity by binding to epithelial

cell surface receptors of the human upper respiratory tract (Gamblin, 2010). The pathogenic mechanism of action resulting in pulmonary inflammation is initiated by HA degradation and cleavage via host proteases (Klenk, 1994). Viral pathogenesis is suggested to largely be facilitated through the host immune response and viral interactions among macrophages, neutrophils and alveolar epithelial cell apoptosis (Fukuyama, 2011). Figure 23 shows a macrophage, a white blood cell, engulfing bacteria.

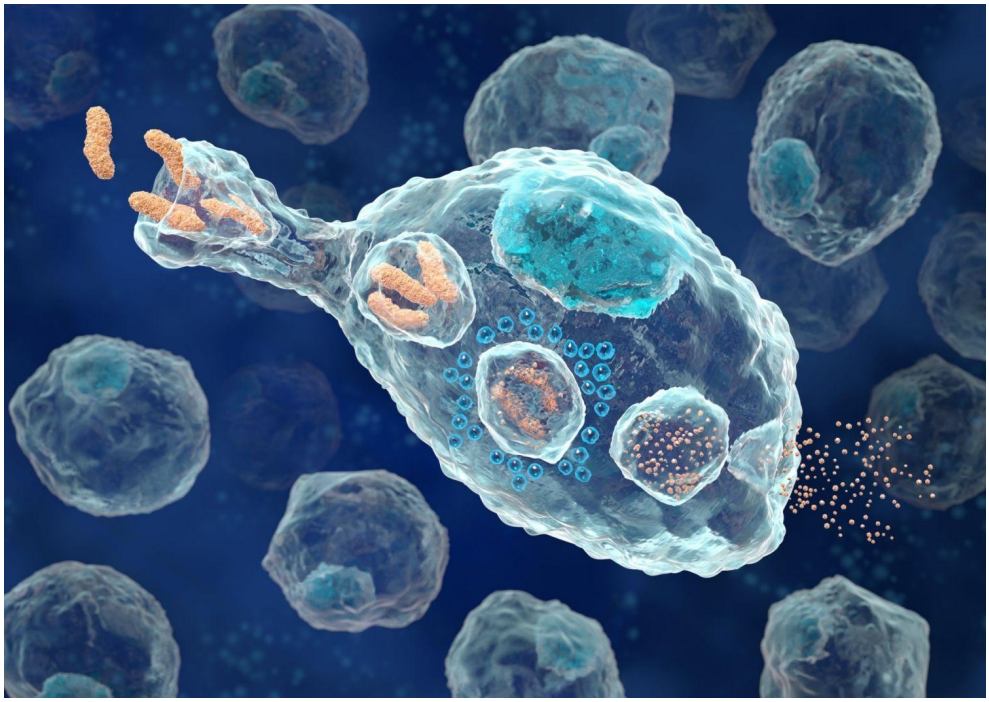


Figure 23. Macrophage Engulfing a Bacterium

Viral pathophysiology can subsequently be approached with the basic understanding that viral pathogenesis is established within the human respiratory tract. Influenza progression is classified with symptoms such as fever and respiratory symptoms, such as coughing or soreness of the throat (Aoki, 2012). These symptoms can also help physicians determine the seriousness of the patient's condition. In order to do so, physicians must know exactly what symptoms patients exhibit and when they appear in relationship to the viral life cycle.

The average incubation stage of influenza disease progression occurs within two days of contact, but can range from 1 to 4 days (CDC, "Clinical", 2016). During this time patient's presentation can be largely asymptomatic, however, is still contagious. Characterization of influenza from other influenza like illnesses is distinguished typically by rapid onset of respiratory and constitutional signs and symptoms (CDC, "Clinical", 2016). Pathophysiological conditions that stimulate recognizable respiratory and global symptoms are a result of the viral reproduction within cells of patient airway in addition to the inflammatory immune response (Bahadoran, 2016).

Symptomatic presentation occurs in uncomplicated patients with influenza for approximately 5 to 7 days after the initial illness presentation (CDC, "Clinical", 2016). This second phase is the period of illness phase (CDC, "Principles", 2012). T-cells of the immune system are reproduced by the millions in order to specifically kill cells infected with the influenza virus. B-cells produce millions of antibodies that bind to the actual virus and kill it. The volume of the cells can swell the lymph nodes of the patient (Lanzavecchia, 1985). T-cells and antibodies travel in the blood to the site of the infection and eliminate the presence of the virus (CDC "Key", 2017). Mucus secretion is triggered for the body to get rid of the cellular debris remaining after the immune response resulting in rhinorrhea and tussis (Discovery, 2000). Even after the virus has been largely eliminated from the body and symptoms have subsided patients are still contagious due to residual traces of virus in their saliva (Rothberg, 2005). Figure 24 illustrates the progression of the influenza virus in the respiratory tract of sick patients.

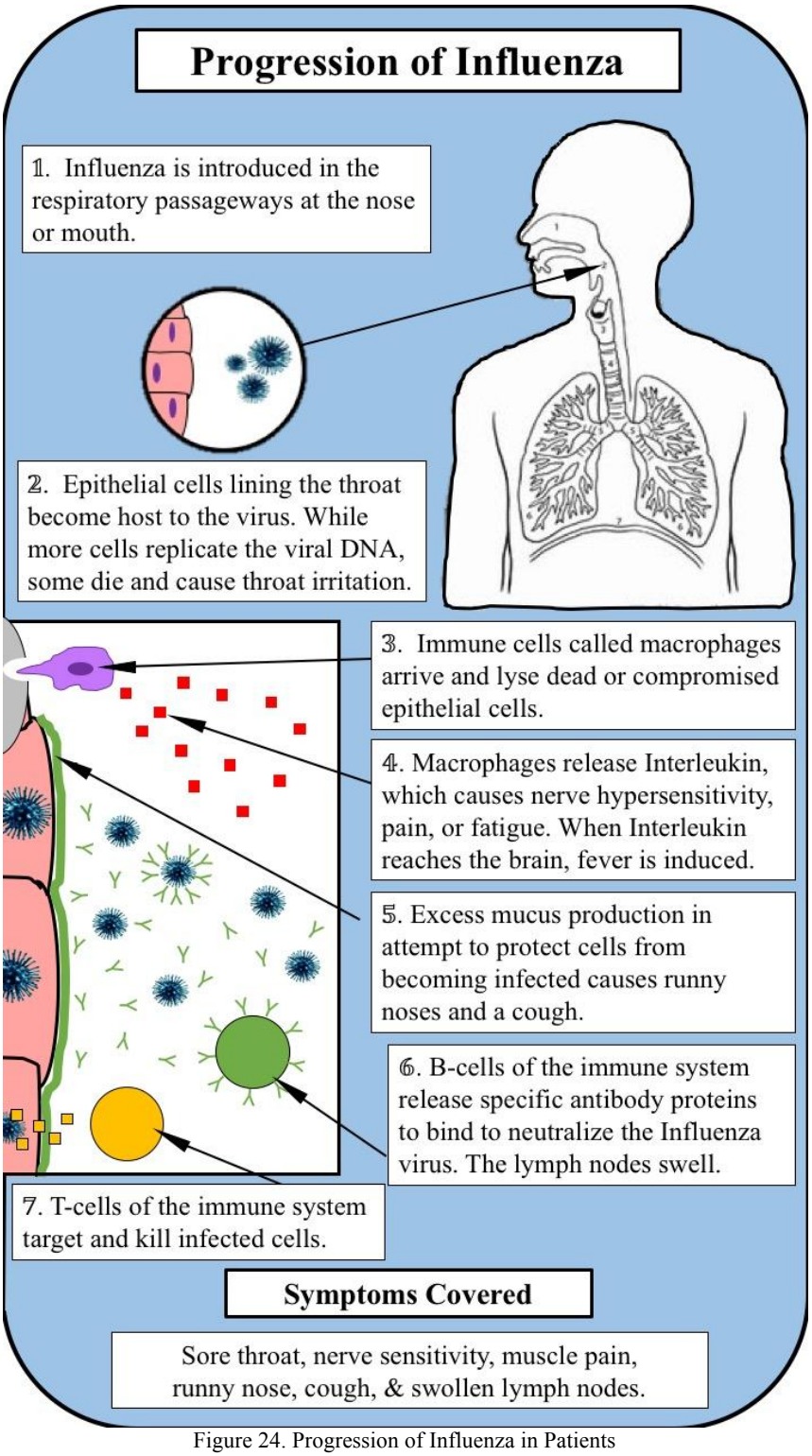


Figure 24. Progression of Influenza in Patients

When symptomatic with influenza, patients typically present with sore throat, fatigue, muscle pain, fever or body chills and a cough (Rothberg, 2005). Depending on the strain of influenza and the physical characteristics of the patient, other symptoms may include: loss of appetite, general feelings of weakness and muscle aches. Other less common symptoms, as well as classification for all the symptoms are presented in Figure 25 (Powers, 2016).

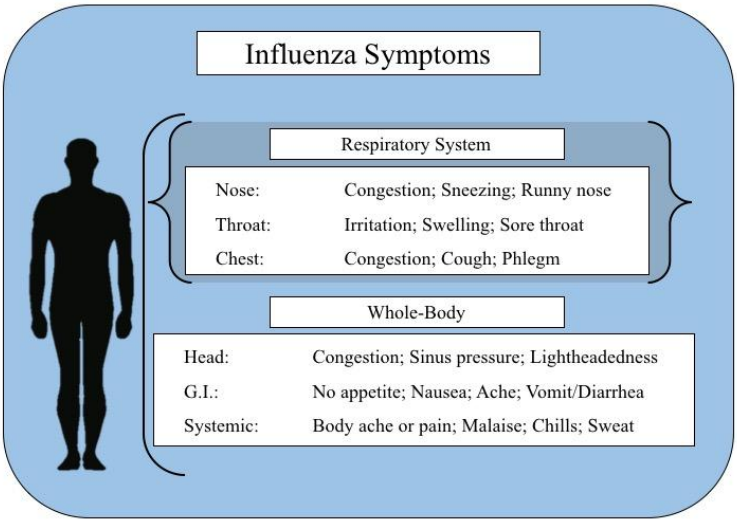


Figure 25. Influenza Symptom Classification

As shown, influenza has the capability to disrupt essentially all parts of the body, but usually is focused on the respiratory system. The most predominate signs and symptoms of influenza is chronic tussis and pyrexia (Monto, 2000). Treatment of these symptoms is rather straightforward - beyond any symptoms suppressors, the patient should get rest and be well-hydrated (Monto, 2000). Unfortunately, since these symptoms are shared by a variety of other diseases, virus and infections, accurate diagnosis of influenza based on symptoms alone is inherently complicated (Monto, 2000).Based on proportional findings of symptoms and corresponding influenza diagnosis the probability of influenza presence can be estimated through probability. When tests were conducted by researchers from the American Medical Association

on a population of individuals suspected to have influenza, it was shown that certain combinations of symptoms are far better at predicting the flu than individual symptoms (Monto, 2000). Table 1 shows a comparison of combinations of symptoms to the Positive Predictive Value (PPV), or the chance of having influenza with the listed symptoms (Monto, 2000). The Negative Predictive Value (NPV), or the chance of not having influenza without the listed symptoms; sensitivity, or the chance of having the symptoms when a patient has influenza and specificity, or the chance of not having the symptoms when the patient does not have influenza.

Table 1. Predictors of Influenza Infection

Symptoms	PPV	NPV	Sensitivity	Specificity
Fever	76.85	49.14	67.79	60.38
Cough	69.43	60.89	93.24	20.41
Fever + Cough	79.04	48.91	63.81	67.19
Fever + Cough (< 36 h)	77.28	51.35	62.32	67.54
Fever + Cough (> 36 h)	85.37	42.33	50.30	80.89
Fever + Cough + Nasal Congestion	81.45	48.21	59.03	73.94
Fever + Cough + Weakness	80.27	47.85	59.80	71.54
Fever + Cough + Muscle Aches	79.11	47.86	61.50	68.54
Fever + Cough + Loss of Appetite	79.04	47.75	61.38	68.45
Fever + Cough + Sore Throat	79.02	45.30	55.51	71.43
Fever + Cough + Headache	78.69	46.81	59.80	68.60

As one can see from the PPV values, the combinations that most likely indicate an influenza infection is a fever and a cough after 36 hours of the symptoms, however, this is not as useful, since individuals must be treated within 48 hours. Furthermore, while all the PPV values are rather high, this study was done on individuals suspected of having the flu, during the flu season, which means that the actual year-round PPVs are probably much smaller. Despite these limitations, practical applications of diagnosis on the premise of empirical patient presentation is effective in relation to seasonal fluctuations in influenza prevalence.

2.4.3 In-Hospital Diagnosis and Molecular Biology

There are multiple testing methods which have been used in hospitals in order to diagnose influenza. The first influenza testing method is RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction). The influenza virus uses RNA as its genetic material, which can be translated directly to protein by the host's ribosomes. The RT-PCR method was subsequently developed to detect viral genetic material. A summary of the RT-PCR method is shown in Figure 26 (New England Biolabs, 2017). First, a patient's flu swap is submerged into PCR buffer. The buffer contains all the necessary ingredients to carry out the RT-PCR. These ingredients include Reverse Transcriptase (RT) (the enzyme that turns influenza RNA into DNA), primers (used to kick off the amplification process), nucleotides (the bases required for the formation of new DNA) and Tag polymerase (the enzyme carrying out the synthesis of the new DNA).

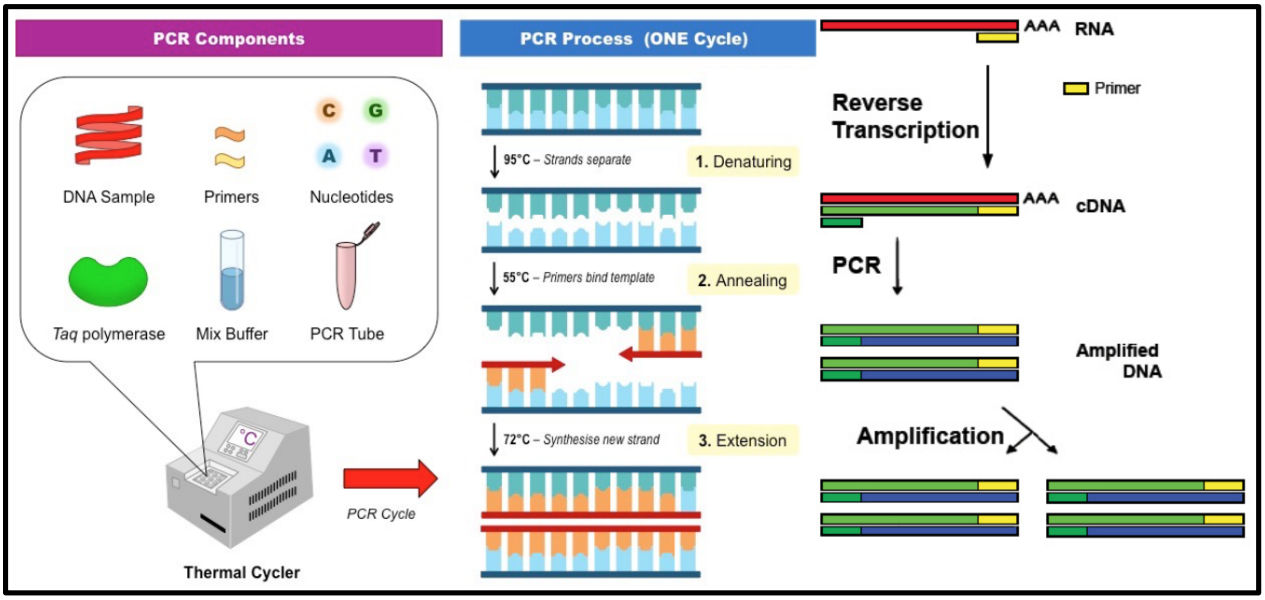


Figure 26. RT-PCR Schematic

The PCR reaction is carried out in a machine called the thermal cycler. This machine varies the temperature on a cycle to perform different tasks. The cycle includes 5 minutes at 50°C, 10 minutes at 94°C (separates the DNA strands); and 42 cycles of 45°C for 1 minute

(primers attach, Taq polymerase makes more copies), 72°C for 1 min, and 94°C for 30 seconds. The use of RT is vitally important because DNA is substantially more stable than RNA which makes it easier to work with and a great diagnostic target. The products of the RT-PCR cannot be visualized with the naked eye. To know if influenza genetic material is present in the patient sample, the RT-PCR products are applied to an electrophoresis gel. A voltage (90V) is then applied to the gel and DNA moves down the electrical gradient. Figure 27 shows an example of the RT-PCR gel results (Hassan et al., 2014). Big, heavy bands on the gel indicates a positive test for the influenza virus. As a way of validating results, these gels are loaded with known influenza negative and influenza positive samples as controls.

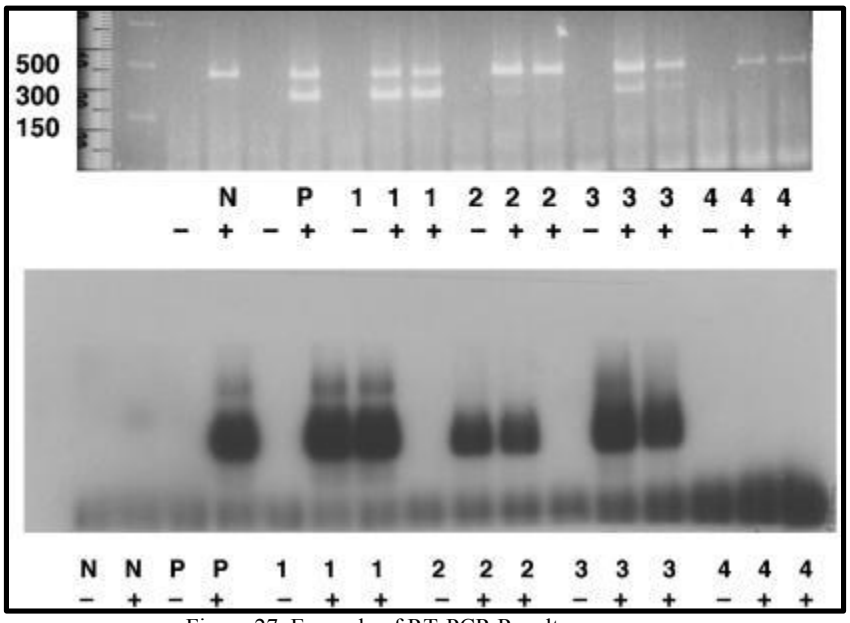


Figure 27. Example of RT-PCR Results

Setting up samples for RT-PCR, loading the gels, and interpreting the results can be cumbersome and requires a tremendous amount of training. In addition, this testing method takes substantially longer than Point of Care (POC) testing methods and is very prone to false results if the samples are not properly prepared or contaminated during the testing process. As seen in Figure 27, the RT-PCR method has many drawbacks and limitations. Some of those drawbacks

include the long sample preparing times, the need for specially trained personnel, the possibility of false test results and the cost of the device. To combat the long sample preparation and testing time and the possibility of false test results, faster and more accurate POC testing devices have been designed and are in use in many hospitals and clinics in the United States. Such devices include the *Becton Dickinson (BD) Veritor System for Rapid Detection of the Flu A+B Immunoassay*, *Sofia Influenza A+B Fluorescent Immunoassay* and the *Alere i System*. These devices have significantly cut down testing times and increased test results accuracy (see Table 2).

Table 2. Comparing RT-PCR with POC Testing Methods

	RT-PCR	*BD Veritor System*	*Sofia System*	*Alere i*
Swap Type	Nasal swab only	Nasal or nasopharyngeal swab	Nasal or nasopharyngeal swab	Nasal swab only
Test Type	RT-PCR	Immunoassay	Immunoassay	Nucleic Acid Amplification
Test Performance	influenza A PPA = N/A NPA = N/A influenza B PPA = N/A NPA = N/A	influenza A PPA = 78.7% NPA = 97.8% influenza B PPA = 74.3% NPA = 99.5%	influenza A PPA = 91.6% NPA = 88.9% influenza B PPA = N/A NPA = N/A	influenza A PPA = 97% NPA = 88% influenza B PPA = 91.2% NPA = 93.8%
Time	2.5 - 4 Hours	10 Minutes	15 Minutes	15 Minutes
Temperature	Room temperature	Room temperature	Room temperature	Orange base must be refrigerated. Test can be conducted at room temperature
Printed Results?	No	No	Yes	Yes
Multiple Tests?	Yes - can set up multiple gels at the same time	Yes	Yes	No
Power Source	N/A	Two batteries	Four AA batteries, AC/DC power adapter	12V DC from external AC/DC power adapter
Other Notes	The PCR machine is very temperature sensitive. Requires a lot of training to prepare samples, load the gels, and interpret the results	Requires user engagement at various stages. Does not have the ability to store test results	Automatically times the test. Does not require user engagement other than initial setup. Can transfer test results to patient record	Requires user engagement at various stages. Requires refrigeration of the orange base

Table 2 compares several key features of RT-PCR, *BD Veritor System, Sofia System* and the *Alere i System*. Table 2 also includes the Positive Percent Agreement (PPA) value and the Negative Percent Agreement (NPA) for the *BD Veritor System, Sofia System*, and the *Alere i System*. The PPA and the NPA are a measure of test performance.

RT-PCR and immunoassays are classical biochemical methods that are still very useful in the world of modern biology and biochemistry. Despite some limitations of these classical methods, POC devices such as the *BD Veritor System for Rapid Detection of the Flu A+B Immunoassay* and the *Sofia Influenza A+B Fluorescent Immunoassay* still rely on these methods, but in a more streamlined and automated fashion. Influenza immunoassays utilize antibodies that attach to antigens on the surface of the virus. The antibodies have a fluorescent marker that gives off a signal once the antibody attaches to an antigen. This fluorescence can be measured and a positive diagnosis can be made based on the presence of fluorescence in the patient sample. An overview of the influenza immunoassay is shown in Figure 28.

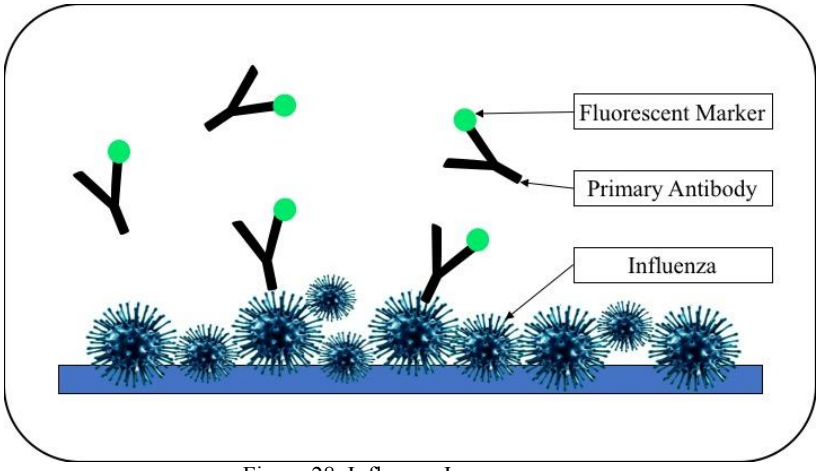


Figure 28. Influenza Immunoassay

The *BD Veritor System for Rapid Detection of the Flu A+B Immunoassay* is a great example of a POC device that utilizes the immunoassay approach. The testing kit comes with the reagent necessary for testing. First, the patient's sample is incubated with the reagent for 10 minutes and then a few drops are added to the test device. Subsequently, the testing device is

inserted into the reader and results are displayed in 10 seconds (see Figure 29; Fisher Scientific, 2018). This two-step process requires user engagement at both steps and thus the *BD System* does not have a "set and read mode."

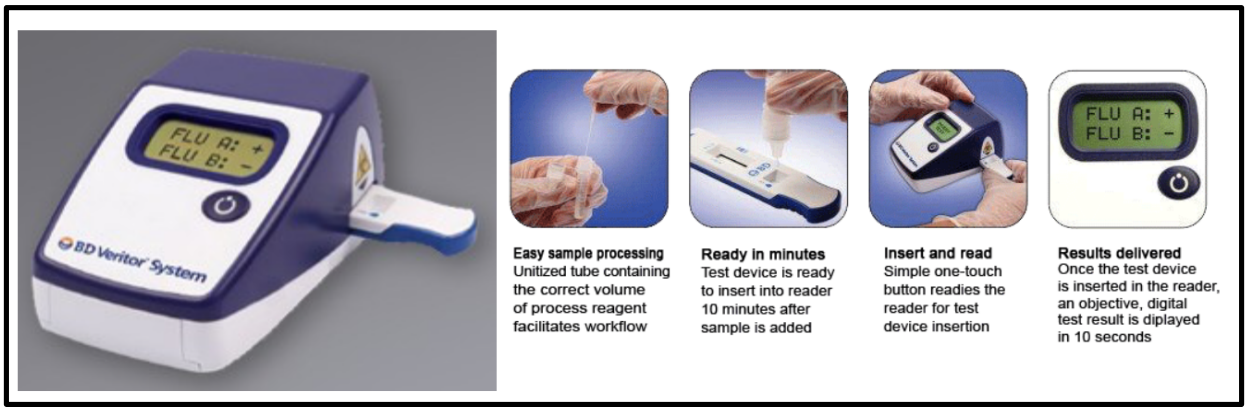


Figure 29. BD Veritor System for Rapid Detection of the Flu A+B

In order to assess the accuracy of the *BD Veritor Rapid Detection System*, three independent studies are utilized to calculate an average of the Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) for both influenza A and B. Table 3 shows the average of the positive predictive value and the negative predictive value for both influenza A and B as calculated from the three independent studies.

Table 3. BD Veritor System for Rapid Detection of the Flu A+B Immunoassay

	Hassan et al., 2014	Dunn et al., 2014	Nam et al., 2014	Average
Sample Size (n)	200	240	250	230
Influenza A				
Positive via RT-PCR	92	48	75	72
Sensitivity	90.2%	93.8%	72.0%	85.3%
Specificity	99.1%	97.9%	57.1%	84.7%
True Positive (n)	83	45	54	61
False Positive (n)	1	4	75	27
True Negative (n)	107	188	100	132
False Negative (n)	9	3	21	11
Positive Predictive Value	98.8%	91.8%	41.8%	77.5%
Negative Predictive Value	92.2%	98.4%	82.6%	91.1%
Influenza B				
Positive via RT-PCR	24	52	75	50
Sensitivity	87.5%	94.2%	69.3%	83.7%
Specificity	100%	100%	100%	100%
True Positive (n)	21	49	52	41
False Positive (n)	0	0	75	25
True Negative (n)	176	188	100	155
False Negative (n)	3	3	23	10
Positive Predictive Value	100%	100%	40.9%	80.3%
Negative Predictive Value	98.3%	98.4%	81.3%	92.7%

The *BD Veritor System* has an average PPV of 77.5% and an average NPV of 91.1% for influenza A and a PPV of 80.3% and a NPV of 92.7% for influenza B. The studies suggest the *BD Veritor System* is slightly more accurate at diagnosing influenza B than influenza A. This is also apparent in the reported specificity. For influenza A, the average calculated specificity across the three independent studies is 84.7% while the specificity for influenza B is 100%. This again suggests that the *BD Veritor System* is slightly better at diagnosing influenza B than influenza A. Overall, the *BD Veritor System* demonstrates great specificity while maintaining high sensitivity (85.3% for influenza A and 83.7% for influenza B) for both positive and negative samples.

Figure 30. Sofia Influenza A+B Fluorescent Immunoassay System

The *Sofia Influenza A+B Fluorescent Immunoassay System* works on the same immunoassay principle the *BD Veritor System* operates on. Although both the *Sofia* and the *BD* system utilize the immunoassay, the Sofia takes 15 minutes to read verses the *BD's* 10 minutes (see Figure 30; Quidel, 2018). However, the *Sofia* is capable of "set and read" which means it only requires user engagement for the initial setup. Once the reader is inserted in the machine, it is read and the test results can be directly integrated into the patient's medical record. Once

again, the team sought to assess the accuracy the *Sofia Influenza A+B Fluorescent Immunoassay* by utilizing seven independent studies to calculate an average of the PPV and the NPV for both influenza A and B (see Table 4).

Table 4. Sofia Influenza A+B Fluorescent Immunoassay

	Lee et al., 2012	Leonardi et al., 2013	Lewandrowski et al., 2013	Dunn et al., 2014	Hazelton et al., 2014	Hazelton et al., 2015	Noh et al., 2015	Average
Sample Size (n)	241	172	2047	240	209	202	394	501
influenza A								
Positive via RT-PCR	73	92	333	48	29	38	196	116
Sensitivity	82.2%	73.3%	78%	95.8%	72.4%	71.4%	74.0%	78.2%
Specificity	100%	96%	100%	91.1%	98.3%	98.2%	95.4%	97%
True Positive (n)	60	72	260	46	21	-	-	91.8
False Positive (n)	0	0	7	17	3	-	-	5.4
True Negative (n)	96	511	1121	175	177	-	-	416
False Negative (n)	73	18	73	2	8	-	-	34.8
Positive Predictive Value	100%	100%	97.3%	73.0%	87.5%	89.3%	94.2%	91.6%
Negative Predictive Value	87.3%	73.9%	93.9%	98.9%	95.7%	94.1%	78.5%	88.9%
influenza B								
Positive via RT-PCR	72	26	245	52	6	12	3	59
Sensitivity	77.8%	59.3%	86%	98.1%	33.3%	33.3%	-	64.6%

From the seven independent studies used, none had any information regarding influenza B. The *Sofia System* has an average of 91.6% PPV and an average of 88.9% for NPV for influenza A. An average PPV and an average NPV could not be calculated for influenza B. For that reason, a direct comparison of the *Sofia's* accuracy between the two types cannot be made. However, based on the independent studies we can conclude that the *Sofia* has a sensitivity of 78.2% for influenza A and a sensitivity of 64.5% for influenza B.

The *Alere i System* works differently than the *BD* and the *Sofia* systems. While other systems utilize the immunoassay approach, the *Alere i* revisits the concept of viral RNA replication as seen in RT-PCR. The major difference between the *Alere's* isothermal nucleic acid amplification technology and RT-PCR is that the *Alere i* operates at one constant temperature and can deliver results in 15 minutes. Once a sample is loaded along with the reagent, a very specific sequence of the influenza genome is recognized and amplified. The amplification process is different in that the *Alere i* uses fluorescent DNA bases. As more copies are made, the

fluorescence of an influenza positive sample increases. If the patient sample is negative for the influenza virus, the machine should not be able to detect any fluorescence. Figure 31 shows the main components of the Alere i system and the overall procedure for loading and reading a patient sample (Alere, 2017).

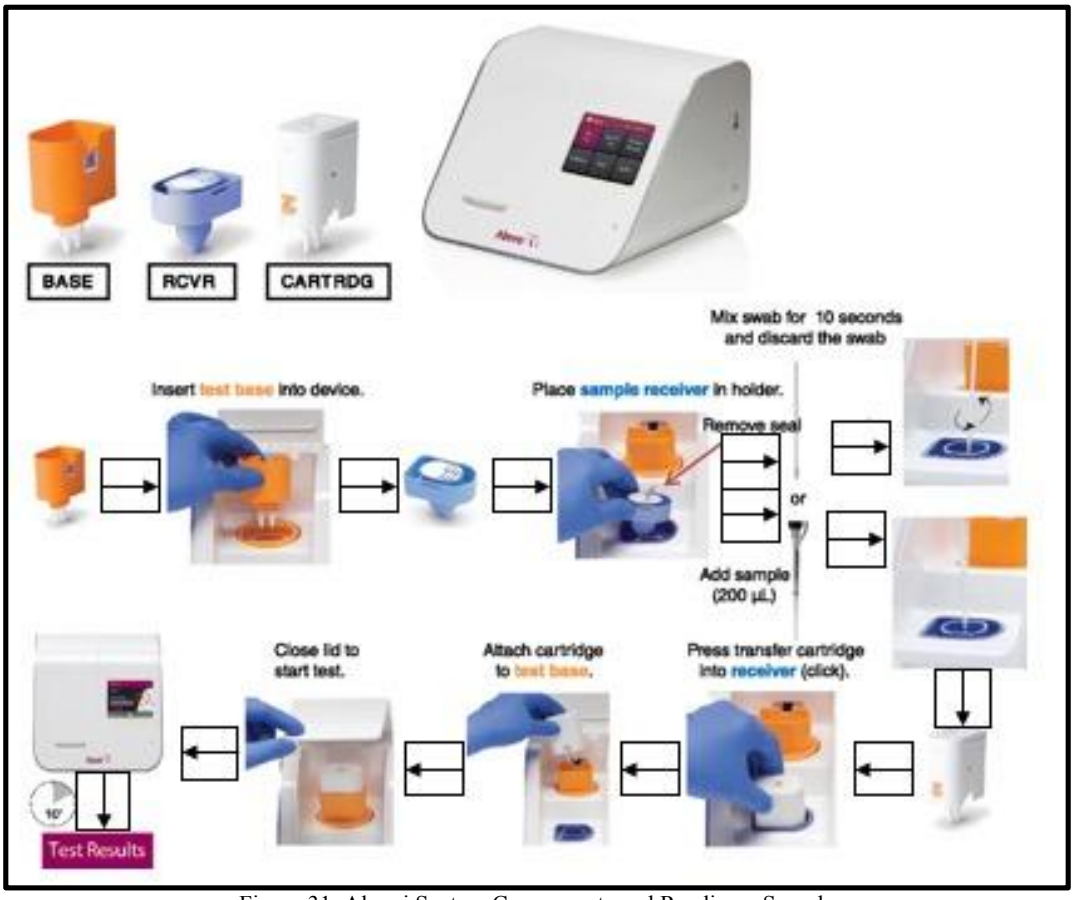


Figure 31. Alere i System Components and Reading a Sample

The orange test base contains the reagent needs for the molecular nucleic acid amplification process. This base must be refrigerated but does not need to be brought to room temperature before inserting into the machine. This base also contains an internal control system used to verify the results. The blue sample receiver (RCVR) accepts the patient sample. The sample is then transferred to the test base via the white transfer cartridge. The sample is then left in the *Alere i* for 10 minutes while the reaction takes place. After the reaction, the results are displayed on the screen. As seen from Figure 31, the *Alere i* requires user engagement at multiple

steps. Once again, six independent studies were used to assess the accuracy of the *Alere i System*. From these studies, an average PPV and an average NPV value was calculated (see Table 5). The PPV for influenza A was 97% while the PPV value for influenza B was 91.2%. This suggests that the *Alere i System* is slightly better as positively diagnosing influenza A than influenza B. The NPV for influenza A is 88% while the NPV for influenza B 93.8%. Lastly, the specificity of the *Alere i* to influenza A is 92.9%, while the specificity to influenza B is 91.8%. This suggests that the *Alere i* has very similar specificity to both influenza A and B.

Table 5. Alere i Results

	Nie et al., 2014	Bell et al., 2014	Chapin et al., 2015	Bell et al., 2014	Jokela et al., 2014	Hazelton et al., 2015	Average
Sample Size (n)	360	236	291	545	140	202	296
influenza A							
Positive via RT-PCR	79	116	180	145	28	36	97
Sensitivity	73.2%	89.4%	93.8%	99.3%	80.0%	77.8%	85.6%
Specificity	100%	98.6%	62.5%	98.1%	98.1%	100%	92.9%
True Positive (n)	79	103	180	145	28	-	107
False Positive (n)	0	2	9	7	2	-	4
True Negative (n)	248	115	15	376	103	-	171
False Negative (n)	29	13	12	1	2	-	11
Positive Predictive Value	100%	98.1%	95.2%	95.4%	93.3%	100%	97%
Negative Predictive Value	89.5%	89.8%	55.6%	99.7%	98.1%	95.4%	88%
influenza B							
Positive via RT-PCR	37	58	45	83	14	12	42
Sensitivity	97.5%	100%	91.8%	97.6%	45.2%	75.0%	84.5%
Specificity	100%	100%	53.6%	100%	98.2%	99.0%	91.8%
True Positive (n)	37	58	45	83	14	-	47
False Positive (n)	0	0	13	0	2	-	3
True Negative (n)	318	174	15	441	107	-	211
False Negative (n)	1	0	4	2	17	-	4.8
Positive Predictive Value	100%	100%	77.6%	100%	87.5%	81.8%	91.2%
Negative Predictive Value	99.7%	100%	78.9%	99.5%	86.3%	98.4%	93.8%

Despite the operational differences between *BD Veritor System for Rapid Detection of the Flu A+B Immunoassay, Sofia Influenza A+B Fluorescent Immunoassay System*, and the *Alere i System*, these POC devices have significantly reduced diagnosis times across healthcare. This allows physicians to appropriately treat patients with influenza.

2.5 Treatment for Positive Influenza Patients

After a patient has been diagnosed with the flu, the physician must decide on how best to treat the patient. The CDC guideline for treatment includes several options. The CDC recommended that physicians either give medications for pain management or if the patient presents to the hospital within the first 48 hours of infection, the can prescribe antivirals (see Figure 33). Physicians can prescribe an antiviral medication such as Tamiflu. In some cases, pain management medications and antivirals can be combined to better manage patient symptoms. The CDC also recommends that the infected patient minimize their contact to uninfected persons, this can be known as "self-quarantine." Self-quarantine along with hand washing and medication compliance is shown to help patients recover faster. The guidelines laid out by the CDC are aimed at preventing the spread of influenza from infected patients to uninfected persons, speeding recovery time, and preventing influenza-related complications.

2.5.1 Treatment Options

When treating patients with the flu, doctors have only several options. First, doctors can prescribe antivirals, such as Tamiflu, seen in Figure 33 (Lim). Doctors can also prescribe medications aimed at controlling the patient's pain. In addition to antivirals like Tamiflu, patients are also encouraged to stay home and drink a lot of fluids. Patients are also encouraged to stay on bedrest to allow their body to recover. Antivirals such as that shown in Figure 32 can reduce viral load thus helping the patient recover faster.

Figure 32. Antiviral Oseltamivir

2.5.2 Treatment Process

Medications such as Oseltamivir, are neuraminidase inhibitors. Neuraminidase is a protein that helps the virus enter the host cell; specifically, it helps open up the cell membrane. Tamiflu inhibits the action of neuraminidase thus the virus cannot get inside the cell (Figure 33; Lim).

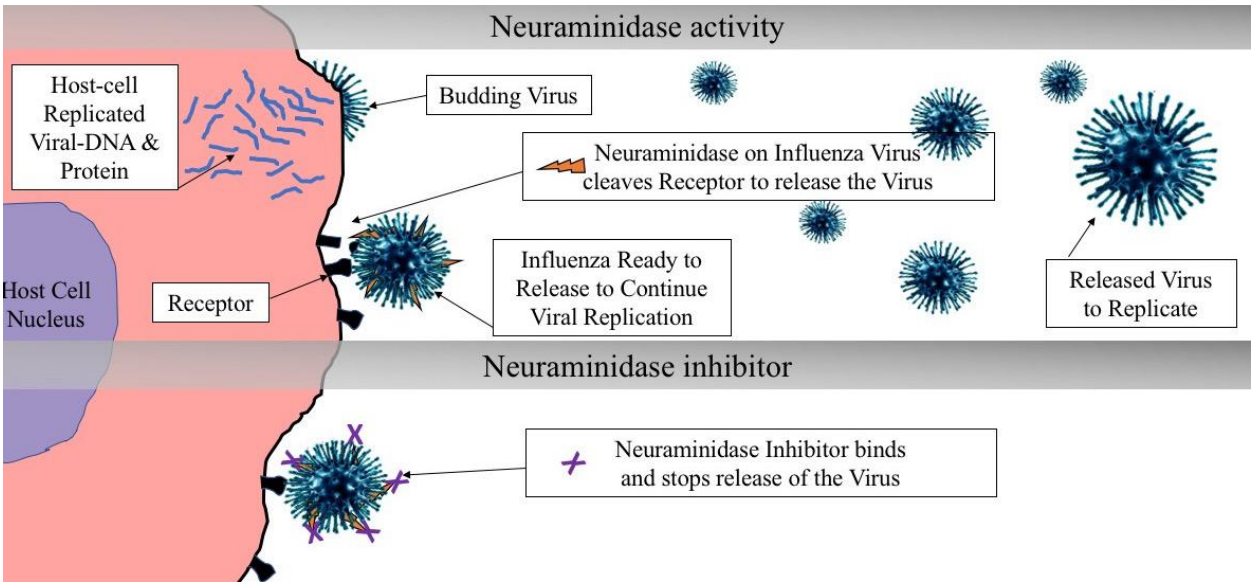


Figure 33. Tamiflu Mechanism of Action

Oseltamivir is the most widely used medication (in the first 48 hours of infection when the virus is still in the incubation period) (CDC, 2013). After the virus gets inside the cell and starts replicating, a neuraminidase inhibitor is no longer effective.

2.5.3 Recovery Process

In healthy adult and pediatric populations, major symptoms of the flu can resolve within 5 to 7 days. Resolution of fatigue and weakness from influenza can range from 1 to 2 weeks after initial infection. If promptly diagnosed and treated with antiviral medications the duration of symptoms and resolution of infection has shown to be improved. Influenza cases resulting in the

development of serious complications require treatment for secondary illness or infection before symptoms are resolved.

Patients afflicted with uncomplicated influenza have resolution of symptoms within the average 5 to 7 day timeframe as previously discussed. Uncomplicated cases of influenza compromise the expected prognosis of healthy adult individuals without pre-existing conditions. Patients that experience complications due to influenza have elevated morbidity and mortality(Rothberg, 2003). Although the death toll fluctuates from year-to-year, from the influenza seasons of 1976-1977 through 1998-1999, the average number of deaths from pneumonia and influenza was 69,140 with a range from 47,133 to 90,895 (Thompson, 2003). In this time frame, the number of deaths increased by 83%. The yearly mortality rates are plotted in Figure 34.

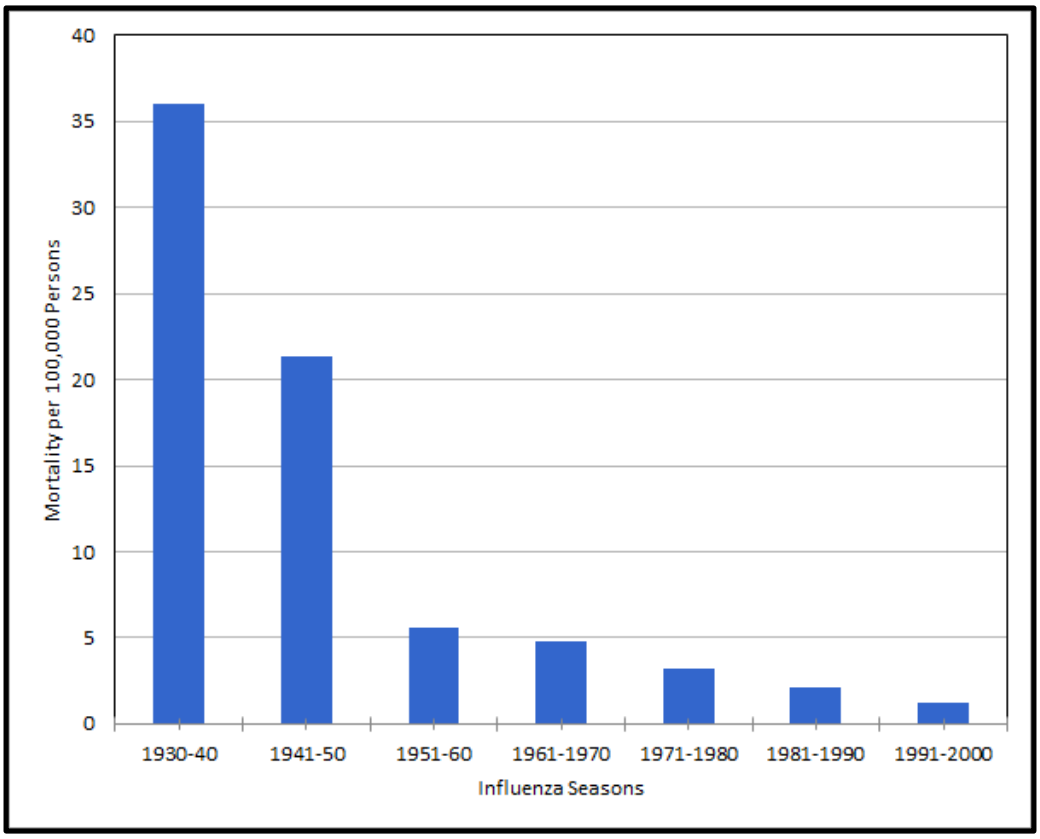


Figure 34. Influenza Mortality Rates per Year

As shown, there was an overall decrease in the deaths per 100,000 cases due to influenza (Doshi, 2008; Armstrong, 2001; CDC, 2001). That number has now stabilized near 1 since the 1981 flu season. As with most studies, large discrepancies can be found in the way things are classified. The study described in Figure 35 identifies people whose cause of death was influenza. Data shown in Figure 35 discards those who died of "complications of influenza" (Doshi, 2008). As such, the actual number of deaths due to the influenza virus is debated.

Individuals in high risk populations particularly pediatric and geriatric cohorts suffer from a predisposition for pneumonia through complications making them susceptible to secondary respiratory syncytial viruses (RSVs) and bacterial infections (Aoki, 2012; Taubenberger, 2007). Patients with asthma tend to experience exacerbation of asthma in addition to hypoxia treated with supplemental oxygen (Aoki, 2012). Pre-existing chronic heart disease has the risk of developing into myocarditis (Aoki, 2012). Other serious complications can include, inflammation of the heart, inflammation of the brain, muscle inflammation and in the most extreme cases, multi-organ failure of the lungs and kidney (Monto et al., 2000). In those cases, influenza can be fatal, although it is estimated that 0.0606% of cases require hospitalization and only 0.0014% of cases are fatal (Viboud et al., 2016). Since not all influenza cases are reported and influenza is typically not recorded on death certificates, it is difficult to determine the exact number of deaths from influenza per year. The WHO estimates that anywhere from 4,000 to 40,000 deaths result from influenza per year (Viboud et al., 2016).

2.6. Materials to Prevent Influenza

In the realm of healthcare and disease prevention and control, material selection is incredibly important. The choices for consideration of materials can be broken down into three main areas, which are the healthcare environment, equipment used and personal protective

equipment (PPE). The rationale for all three of these areas is different based on their intended role in the healthcare system. The CDC issues a paper called the *Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings* (Siegel et al, 2007). It is an intentionally generic document which provides guidance on how to limit exposure to infectious disease in all three of these areas.

In general, the material choice is governed by two factors. The first is that it must be FDA and ISO 10993 compliant. This means that the material itself must be proven and accepted to be biocompatible with human contact for the intended application. Secondly, the material must be easy to clean and disinfect. From there, the desired characteristics of the material can be selected for the given medical application. For rapid testing systems such as the *Alere i* system to work effectively, it is important to have the appropriate material considerations in place.

2.6.1 Environment

The hospital environment plays a large role in public health. A high number of individuals move through common spaces on a daily basis. For this reason, cleaning and disinfection of various surfaces in patient care areas is essential. Specifically, *Isolation Precautions* highlights the need for frequently touched surfaces, such as bed rails, bedside tables, commodes, door knobs, sinks, surfaces and equipment in close proximity to the patient to be cleaned regularly (Siegel et al, 2007).

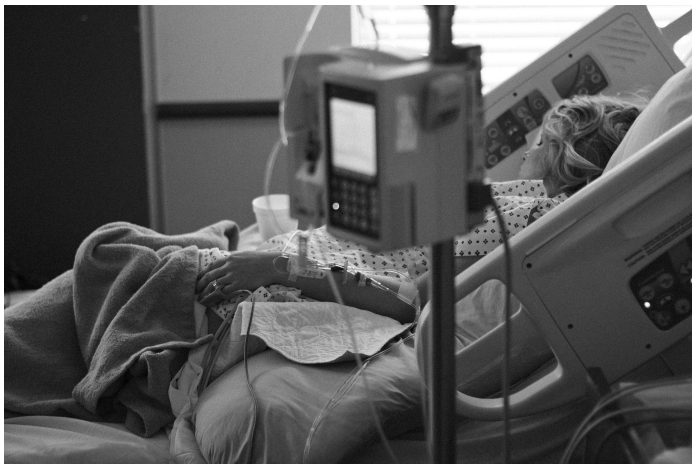


Figure 35. Patient in Hospital

During an uptick of influenza occurrences, it is recommended that cleaning procedures should be reviewed. “EPA-registered disinfectants or detergents/disinfectants that best meet the overall needs of the healthcare facility for routine cleaning and disinfection should be selected” (Siegel et al, 2007).

Detailed recommendations for disinfection and sterilization of surfaces and medical equipment that have been in contact with tissue or body fluids, and for cleaning of blood and body substance spills, are available in the *Guidelines for Environmental Infection Control* in the CDC *Health-Care Facilities and in the Guideline for Disinfection and Sterilization*.

OSHA offers several recommendations from an engineered environment and workplace control perspective when it comes to limiting the impact of influenza in the hospital environment. The first is to modify patient intake and triage areas by creating a barrier or partition between workers and patients. This is known to effectively reduce the initial risk that could be created by having a patient who has yet to be diagnosed inadvertently infecting others. The second recommendation is along the lines of patient placement, whereas patients should be cohorted appropriately. The third recommendation is that infected patients should have limited

transportation. This means that procedures are preferred to occur bedside where the patient is located, instead of transporting the patient around the facility. Limiting transportation effectively reduces the risk that the patient might contaminate others along the uncontrolled travel route. All of these recommendations are integral to limiting the impact of influenza; furthermore, these recommendations can be positively affected by rapid testing devices positively identifying patients who would qualify for these considerations.

2.6.2 The Environment Needed for Rapid Testing Systems

In order for the *Alere i* and similar instruments to be used reliably and according to the procedure outlined in its user manual, there are several environmental conditions that must be satisfied. To begin with, the *Alere i* system, according to its user manual, is rated to operate at room temperature. It is International Protocol (IP) 20 certified, meaning that the device enclosure is able to protect components from touch forces, but is not waterproof. The *Alere i* can be cleaned using 70% ethanol or 10% bleach solution, on a damp, lint free cloth, according to the user manual. Alere recommends that the exterior instrument surfaces and the surfaces visible under the open lid be cleaned daily. They also recommend to clean surrounding bench area and to clean instrument and surrounding areas immediately after possible patient sample contamination. Alere recommends that disposal of all contaminated waste from testing to occur according to federal, state, and local requirements. Beyond these requirements, the device is designed to work in a number of operational environments from clinics, hospitals, or mobile applications.

2.6.3 Personal Protective Equipment

Personal Protective Equipment (PPE) refers to a variety of barriers and respirators used either alone or in conjunction with one another in order to protect an individual from contact with infectious agents. The selection of PPE is based on the nature of the patient interaction and the anticipated modes of transmission. In the case of influenza, the United States Department of Labor Occupational Safety and Health Administration (OSHA) recommends the use of several different types of equipment. This includes gloves, gowns, face shields and potentially respirators. More specifically, gloves are almost always indicated as standard precaution when dealing with patients. They help to protect against direct and indirect transmission of influenza. Gowns are considered appropriate when clothes could be soiled with bodily fluids. The Department of Health and Human Services Pandemic Influenza Plan does not specifically call for the use of face shields or goggles, such as those worn in Figure 36. However, when there is a risk of sprays or splatters of infectious material within six feet of a healthcare worker, eye protection is appropriate.

Figure 36. Individual Wearing PPE

Finally, in the case of pandemic influenza specifically, droplet transmission is a major concern. In these instances, such as seasonal influenza, a respirator is appropriate. A respirator is "a personal protective equipment that is worn on the face, covers at least the nose and mouth, and is used to reduce the wearer's risk of inhaling hazardous gases, vapors, or airborne particles" (OSHA 2017). Once a respirator has been worn near an infected individual, it should be considered contaminated and disposed.

2.7. Summary

Influenza is not a disease that is confined to a world region or a time in history. It has consistently proven itself to be a virus that is capable of thriving in a wide variety of environments and surviving in some of the harshest conditions on earth. In the worst case, as seen with the outbreak of influenza in 1918, it infected individuals on remote Pacific Islands and survived in Antarctica. To underestimate its resilience and the threat that this virus poses to humanity would be a tragic mistake. While the flu is seen as a common disease, it can have

devastating impact when treatment is neglected. In 1918, 50 million men, women and children were killed due to the influenza virus in a single epidemic. These numbers have been far from matched in the last century, however, even today there exist strains of the virus that wields a mortality rate significantly more devastating than the H1N1 strain.

The mortality of the virus, however, is not the sole determiner of death rate. There are a wide variety of options for limiting its spread, which in turn, lowers the overall death rate. These measures have been historically proven to aid in disease treatment and prevention. One reason the 1918 strain was so deadly was that it was allowed to spread unchecked for a significant amount of time. It was the mortality rate of the virus, coupled with the lack of knowledge that allowed so many individuals to become infected. Today, we have a far better understanding of the virus, including the manner in which it spreads. Recognizing that the virus is transmitted between people directly, through contact with surfaces that infected individuals touched and by aerosol droplets, which are expelled by the infected host and later deposited in the respiratory tract of a susceptible host, allows medical professionals and scientists to develop state of the art technological devices and new preventative measures to prevent its spread. Limiting the number of people who become infected has a direct influence on the threat of the virus.

While research is vital to our understanding of the disease and gets us ever closer to preventing it for good, it is not the solution to the present-day task of limiting the spread of the virus. In this regard, we turn to the physical measures being taken by Governments and medical professionals around the world. One of the most effective methods for preventing the disease is public awareness. In the United States, the Center for Disease Control has dedicated an astronomical amount of resources to educating the public on all aspects of the disease. This

education includes symptoms of the disease, environmental conditions for limiting infection and proper sanitary methods for limiting its spread. With this knowledge, each person is encouraged to do his or her part to help contain the disease and limit its impact on society. Another common method for protecting the populace is the administration of vaccines. The primary expected stain has to be identified by CDC and WHO scientist's months before its arrival and such estimations are not always accurate. When this happens, it can leave the populace with a false sense of security surrounding the disease. Finally, when patients do fall ill with the disease, the medical community is becoming far better able to handle the situation without putting other patients in the vicinity at a heightened risk for exposure. This risk is limited by isolating individuals who are suspected of having the flu. Some institutions have gone as far as having a separate entrance and waiting room for individuals suspected of being infected. Similar to other methods of prevention, this is not a perfect method. There are cases where individuals who are not infected with the flu are mistakenly suspected as such. When this happens, the non-infected individuals can be mixed in with the infected individuals and become infected themselves.

Diagnosing influenza can be a complicated process. In the home setting, patients can look for a rapid onset of flu like symptoms, including fever and coughing. However, this method is not considered to be very accurate. In order to effectively diagnose a patient with influenza, he or she must be evaluated by a medical professional. Historically, clinical determinations without the use of a viral culture is largely inaccurate. The influenza virus presents with a rapid onset of symptoms that are extremely similar to several other upper respiratory diseases. In order to make an accurate determination for the patient, health care professionals need to use more scientific methods of diagnosis. This is where technological advancements help in flu prevention. Newer

diagnosing methods are becoming faster and more accurate. The *Alere i* system, for example can accurately determine if a patient has the flu in 15 minutes.

Prevention of the flu can be widely limited through simple actions taken by individuals. The process of self-quarantining is an extremely effective way of preventing infected individuals from infecting healthy hosts. Further methods, including sanitizing surfaces will help to limit non-contact transmission. Proper hand washing, and hygiene will help prevent the spread of the disease through direct contact. It is also possible to maintain environmental ranges that kill the airborne virus particles in the shortest amount of time.

As always however, there is no prescriptive process for preventing the spread of the virus. As such, it is important that each individual do his or her part to help contain its spread. Healthcare professional need to be vigilant in their interaction with potentially infected individuals use the proper protective equipment and effectively use technology that can quickly and accurately identify people with influenza. The combination of these methods has proven to have a significant impact on preventing the disease from spreading. Through proper implementation and awareness, one can collectively limit the spread and effectiveness of the disease in communities.

Chapter 3. Innovation

3. Introduction

Given the danger of large-scale influenza outbreaks, it is necessary for humanity to create and enforce a variety of measures to maintain the public health. Over the past centuries, human society has developed practices to keep our surrounding environment as clean as possible which helps limits the exposure to infectious diseases. While traditional cleaning methods do remove a significant proportion of the microorganisms, the remaining microbes still possess the ability to infect humans. Lately, more sophisticated methods have been developed to remove all microorganisms as well as special materials which do not support the microbial growth.

In addition to individual effort to keep the environment clean, it is also the responsibility of the government and other health organizations to inform and educate the population. These groups use a variety of different methods to teach good behavior and practices to the population which in turn keeps the spread of influenza and other infectious diseases down. These organizations also take a more active stance in reducing the spread of influenza by isolating infected individuals and using the latest technology to detect and combat influenza. For example, the use of early detection devices allows the identification of an infected individual before they become infectious. Other methods are also used to diagnose and detect influenza, studying the patients' symptoms as well as their daily habits and who they came into contact with can be used to predict if a patient has influenza.

Patient education is also a vital part of helping to understand influenza. For that reason, this IQP created an online Influenza Data Center (IDC), which can be accessed through www.MIRADlabs.edu. The IDC provides patients with a threat level map for every state based

on CDC weekly CDC data as derived in Section 3.2.2. Patients can also click on the map to learn about the influenza threat level for their state and get CDC advice on how to stay healthy and avoid getting the flu. Lastly, the IDC provides patients with information regarding influenza history, transmission, prevention, diagnosis, and treatment.

3.1. Influenza Data Center (IDC) Home Page

The IDC can be accessed from either a computer or a cell phone allowing for easy access to all patients regardless of location. The homepage of the IDC website is shown in Figure 78. From the homepage, patients can navigate to the threat map by clicking the "VIEW THREAT" button. Alternatively, patients can select a specific state from the dropdown menu. From the home page, patients can also access information about influenza history, transmission, prevention, diagnosis, and treatment by using the appropriate button on the bottom of the IDC webpage.

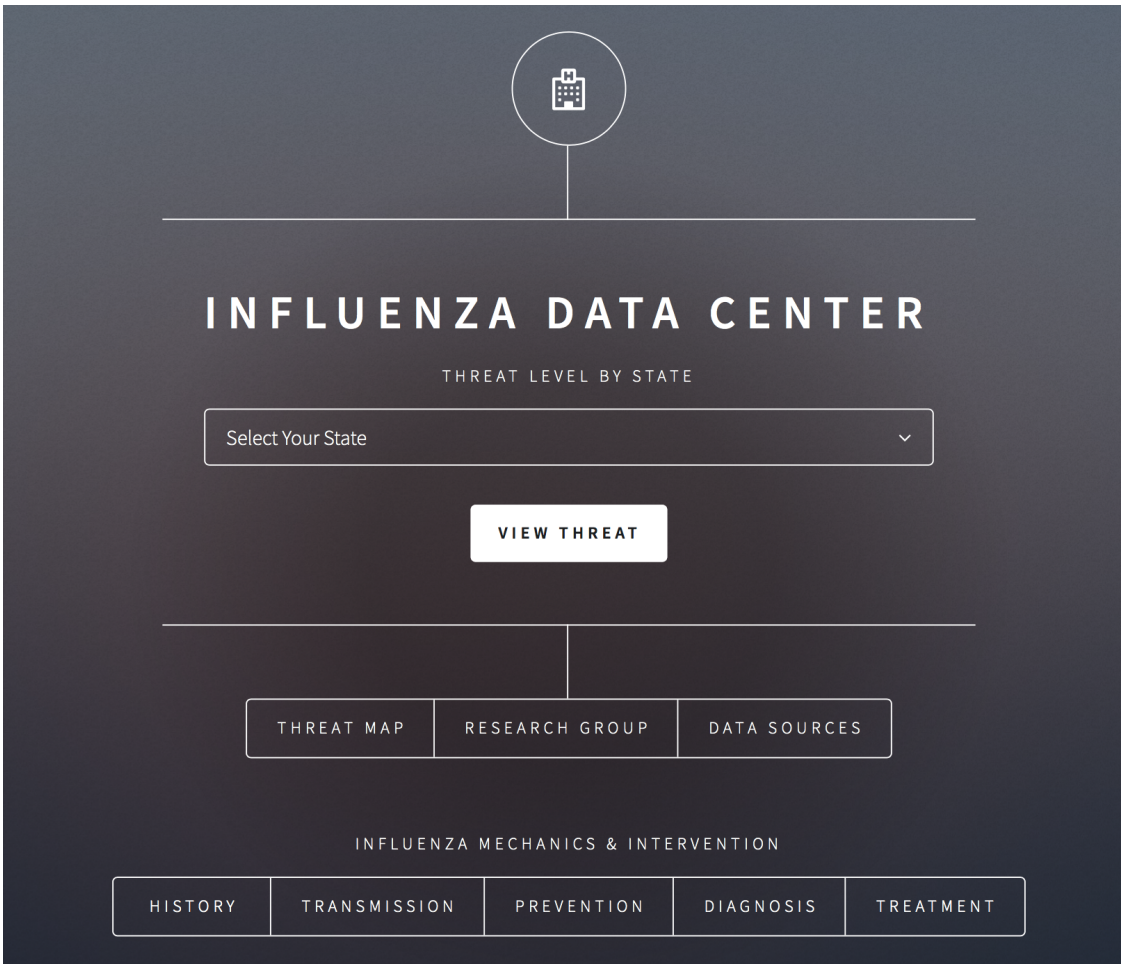


Figure 37. Influenza Data Center (IDC) Home Page Navigation

3.1.1. Influenza Threat Map

Clicking on the "VIEW THREAT" button on the IDC homepage brings patients to a United States influenza threat map, shown in Figure 38. This map is updated automatically weekly based on CDC data and thus patients are always getting the most up-to-data data. Red indicates widespread influenza, yellow is regional, brown is local activity, green is sporadic activity, and light blue is no activity.

Figure 38. United States Influenza Threat Map

Using the threat map shown in Figure 38, patients can click on any state they like to get information regarding influenza activity and CDC recommendations based on their local activity. An example is shown in Figure 39. As shown, the data is always kept up-to-data by automatically updating from CDC data and gives patients easy recommendations to follow to help deal with their local activity.

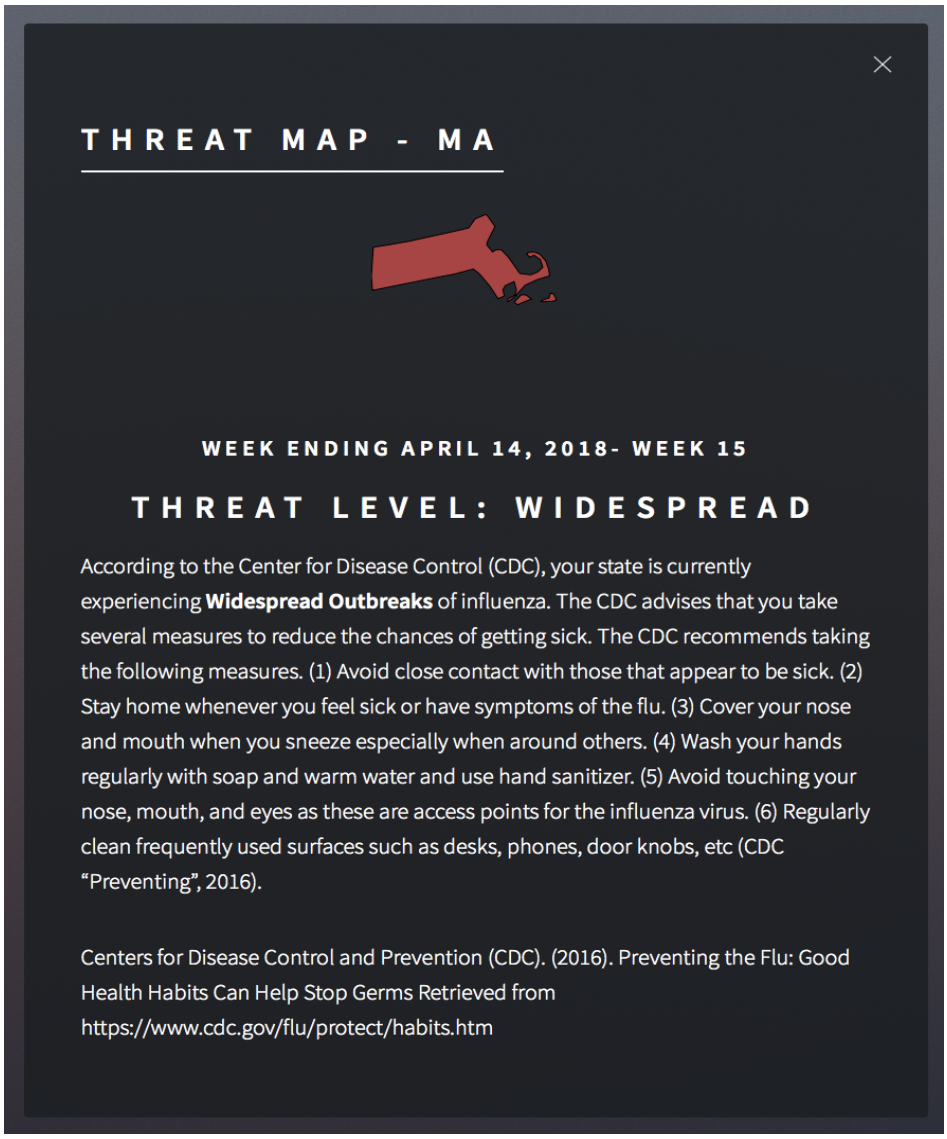


Figure 39. IDC Massachusetts Influenza Activity and CDC Recommendations

3.1.2. IDC Influenza Mechanisms and Intervention Tabs

The IDC contains an additional five tabs meant to provide patients with information regarding influenza history, transmission, prevention, diagnosis, and treatment, distilled from Chapter 2 of this project. Figures 40 and 41 show examples of the diagnosis and treatment tab, respectively. Patients can scroll through these pages to learn about the influenza and all relevant information.

DIAGNOSIS

There are multiple testing methods which have been used in hospitals in order to diagnose influenza. The first influenza testing method is RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction). The RT-PCR method was developed to detect viral genetic material. A summary of the RT-PCR method is shown in Figure 1.

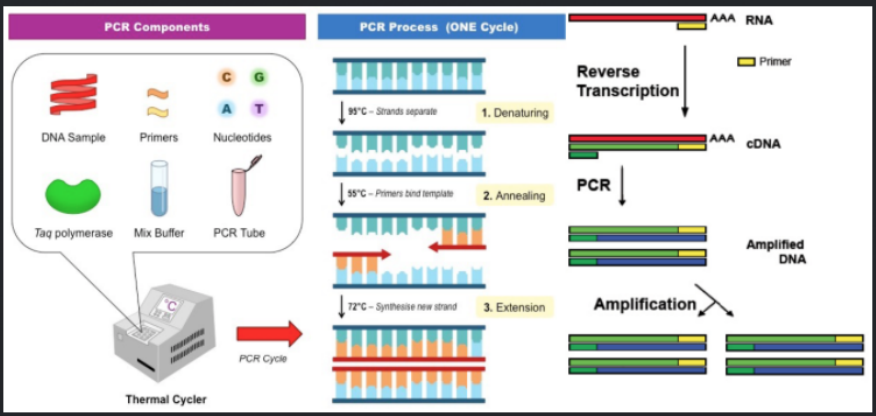


Figure 1. RT-PCR Schematic (New England Biolabs, 2017)

The PCR reaction is carried out in a machine called the thermal cycler. This machine varies the temperature on a cycle to perform different tasks. 50°C for 5 min, 94°C for 10 min, 42 cycles of 45°C for 1 minute, 72°C for 1 minute, and 94°C for 30 seconds. The products of the RT-PCR cannot be visualized with the naked eye. To know if influenza genetic material is present in the patient sample, the RT-PCR products are applied to an electrophoresis gel. A voltage (90V) is then applied to the gel and DNA moves down the electrical gradient. Figure 2 shows an example of the RT-PCR gel results. Big, heavy bands on the gel indicates a positive test for the influenza virus. As a way of validating results, these gels are loaded with known influenza negative and influenza positive samples as controls.

Figure 40. Example of the IDC Diagnosis Tab

TREATMENT

TREATMENT OPTIONS

When treating patients with the flu, doctors have only several options. First, doctors can prescribe antivirals, such as Tamiflu. Doctors can also prescribe medications aimed at controlling the patient's pain. In addition to antivirals like Tamiflu, patients are also encouraged to stay home and drink a lot of fluids. Patients are also encouraged to stay on bedrest to allow their body to recover.

TREATMENT PROCESS

Medications such as Oseltamivir, are neuraminidase inhibitors. Neuraminidase is a protein that helps the virus enter the host cell; specifically, it helps open up the cell membrane. Tamiflu inhibits the action of neuraminidase thus the virus cannot get inside the cell (see Figure 34).

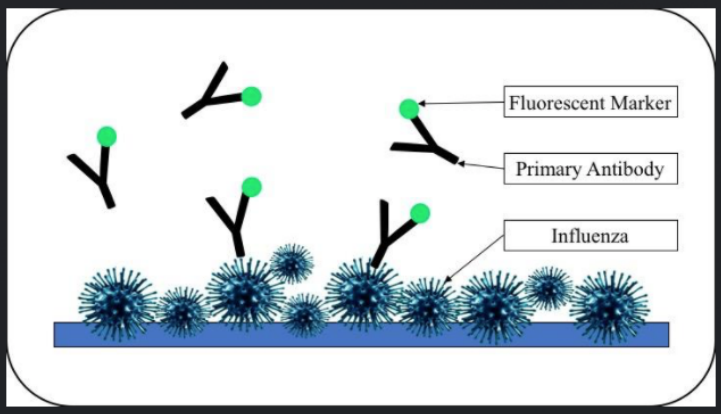


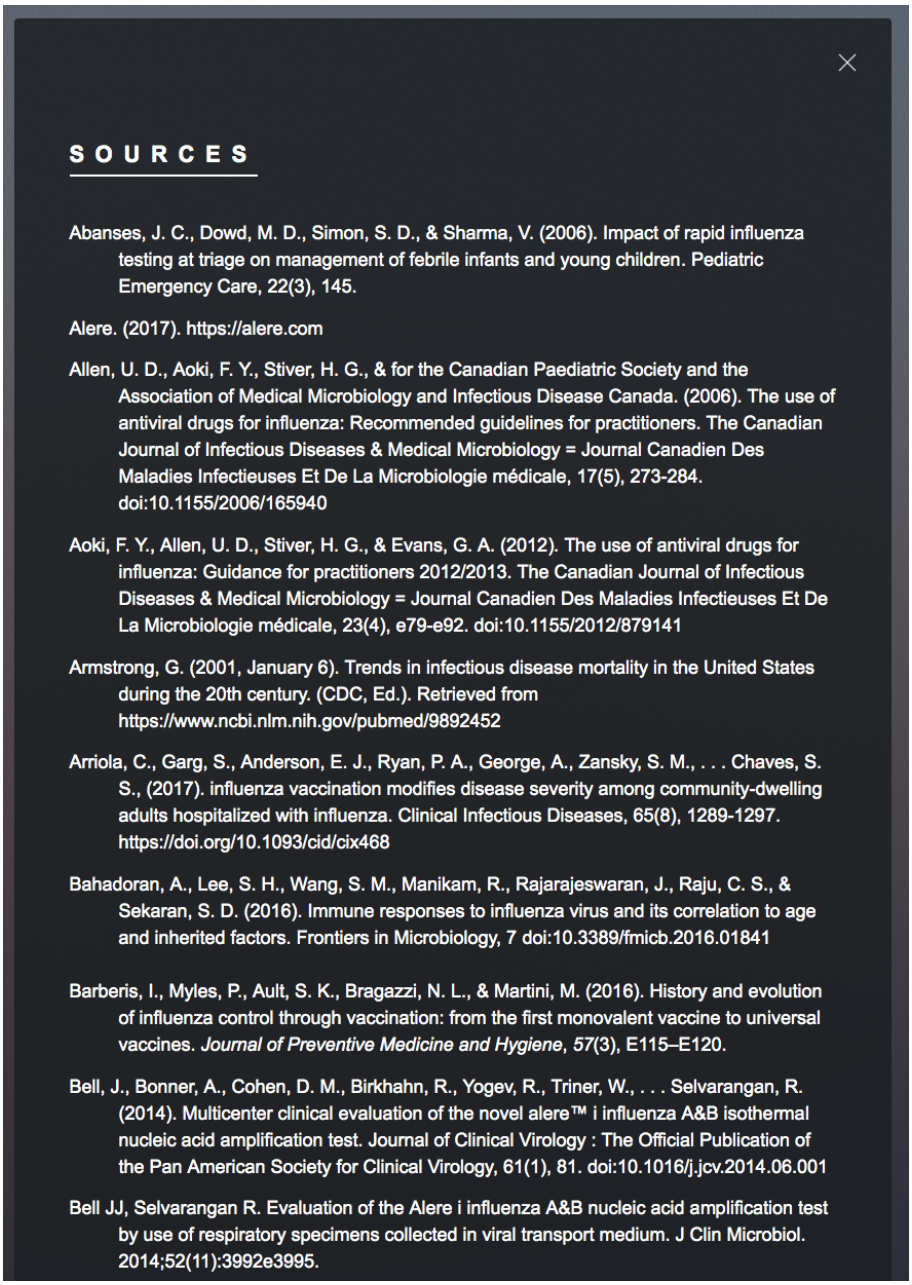
Figure 34. Tamiflu Mechanism of Action (Lim)

Oseltamivir is the most widely used medication (in the first 48 hours of infection when the virus is still in the incubation period) (CDC, 2013). After the virus gets inside the cell and starts replicating, a neuraminidase inhibitor is no longer effective.

Figure 41. Example of the IDC Treatment Tab

3.1.3. IDC Data Sources

All data posted on the IDC website has been verified through multiple peer review sources and the CDC. The IDC provides patients with those sources (see Figure 42) and encourages all readers to access these articles to learn more about influenza.



SOURCES

Abanses, J. C., Dowd, M. D., Simon, S. D., & Sharma, V. (2006). Impact of rapid influenza testing at triage on management of febrile infants and young children. Pediatric Emergency Care, 22(3), 145.

Alere. (2017). https://alere.com

Allen, U. D., Aoki, F. Y., Stiver, H. G., & for the Canadian Paediatric Society and the Association of Medical Microbiology and Infectious Disease Canada. (2006). The use of antiviral drugs for influenza: Recommended guidelines for practitioners. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie médicale, 17(5), 273-284. doi:10.1155/2006/165940

Aoki, F. Y., Allen, U. D., Stiver, H. G., & Evans, G. A. (2012). The use of antiviral drugs for influenza: Guidance for practitioners 2012/2013. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie médicale, 23(4), e79-e92. doi:10.1155/2012/879141

Armstrong, G. (2001, January 6). Trends in infectious disease mortality in the United States during the 20th century. (CDC, Ed.). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9892452

Arriola, C., Garg, S., Anderson, E. J., Ryan, P. A., George, A., Zansky, S. M., . . . Chaves, S. S., (2017). influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. Clinical Infectious Diseases, 65(8), 1289-1297. https://doi.org/10.1093/cid/cix468

Bahadoran, A., Lee, S. H., Wang, S. M., Manikam, R., Rajarajeswaran, J., Raju, C. S., & Sekaran, S. D. (2016). Immune responses to influenza virus and its correlation to age and inherited factors. Frontiers in Microbiology, 7 doi:10.3389/fmicb.2016.01841

Barberis, I., Myles, P., Ault, S. K., Bragazzi, N. L., & Martini, M. (2016). History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. *Journal of Preventive Medicine and Hygiene*, *57*(3), E115–E120.

Bell, J., Bonner, A., Cohen, D. M., Birkhahn, R., Yogev, R., Triner, W., . . . Selvarangan, R. (2014). Multicenter clinical evaluation of the novel alere™ i influenza A&B isothermal nucleic acid amplification test. Journal of Clinical Virology : The Official Publication of the Pan American Society for Clinical Virology, 61(1), 81. doi:10.1016/j.jcv.2014.06.001

Bell JJ, Selvarangan R. Evaluation of the Alere i influenza A&B nucleic acid amplification test by use of respiratory specimens collected in viral transport medium. J Clin Microbiol. 2014;52(11):3992e3995.

Figure 42. IDC Data Sources

3.2. Influenza Transmission Solutions

Outside of the four pandemics in the last century, there have been repeated, yearly epidemics that affect fewer people in an isolated region. These isolated occurrences are what is commonly referred to as, the "flu season." In the United States, this typically runs from October through May (CDC, 2017). These patterns, shown in the section on CDC FluView Maps (3.1.2), are clearly evident, yet they have no scientific explanation (Tamerius et al., 2012). We can, however, limit the spread of infections through proper cleaning practices. The CDC recommends that people clean and disinfect commonly touched surfaces and routinely clean and disinfect all surfaces (CDC, "How to Clean", 2017). The CDC also recommends that individuals avoid close contact with sick victims, stay home when sick to prevent spreading the illness and clean your hands often (CDC, "Stopping the Spread of Germs", 2017).

3.2.1. Recommended Current Cleaning Practices

Influenza can survive on surfaces and the human skin for an extended period of time. For that reason, the CDC recommends that all frequently used surfaces be properly cleaned. According to the CDC, the single most effective way to clean one's skin and protect against the virus is handwashing with soap and warm water (see Figure 43; CDC "Preventing the Flu", 2018).

Figure 43. CDC Recommends Handwashing

In addition to handwashing, the CDC recommends that all commonly used surfaces be cleaned frequently. Surfaces such as phones, door knobs, desks, keys, light switches, elevator buttons, keyboards, laptops, etc. can all harbor the influenza virus (See Figure 44). For that reason, these surfaces should be cleaned with common household products to prevent the spread of the flu.

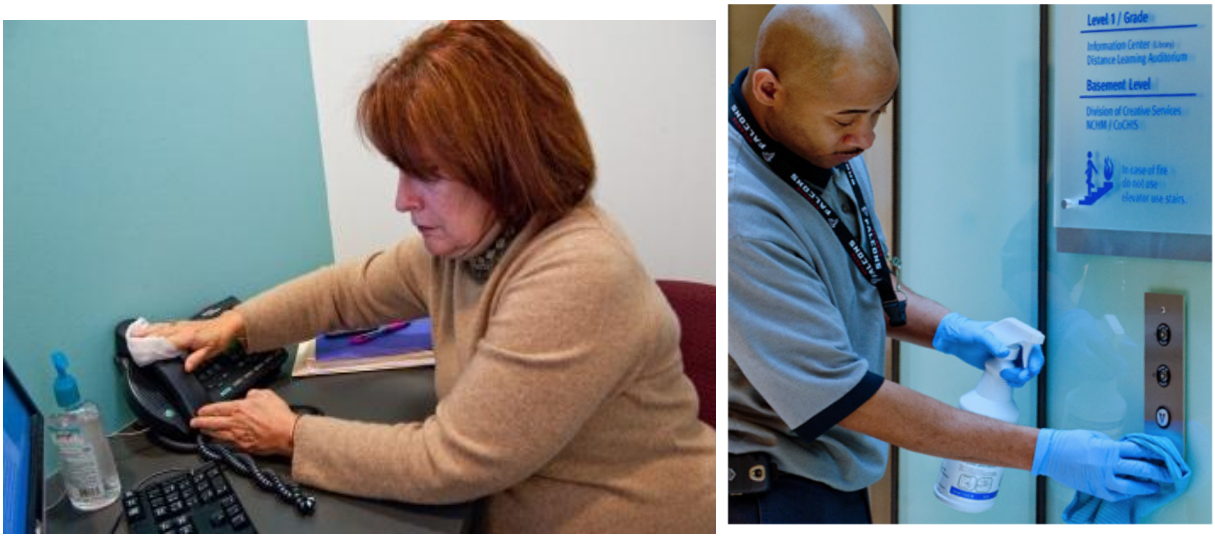
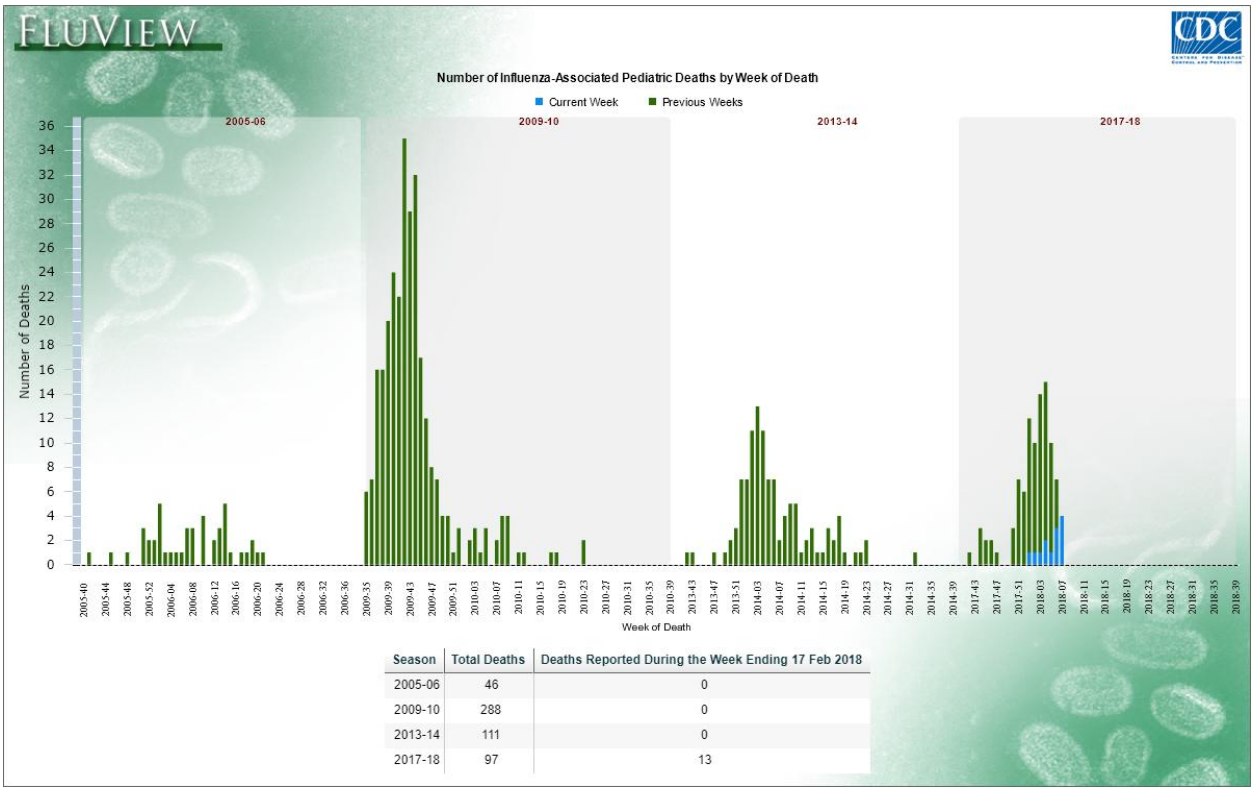


Figure 44. Cleaning Commonly Used Surfaces

The cleaning of these surfaces frequently with household products can help control the spread of the virus especially in commonly congested office spaces or any enclosed space.

3.2.2. CDC Data

For the past two decades, the Center for Disease Control has been publishing data about influenza on a weekly basis. The following figures signify the cyclic nature of influenza outbreaks, as well as, highlight key patterns of the virus. Figure 45 shows the yearly spike in influenza cases each year, be documenting the numbers of pediatric deaths each week in the United States during the respective year's flu season.



Season	Total Deaths	Deaths Reported During the Week Ending 17 Feb 2018
2005-06	46	0
2009-10	288	0
2013-14	111	0
2017-18	97	13

Figure 45. Weekly Influenza Deaths over Individual Year at Four Year Intervals

The figure specifically shows the flu seasons of 2005-2006, 2009-2010, 2013-2014 and 2017-2018. As we can see, the 2009-2010 season stands out as significantly higher than the others, as this was the most recent influenza pandemic, the H1N1 Swine Flu.

Figure 46 shows that over the same time periods described above, the gender breakdown for death rates if roughly equal each year.

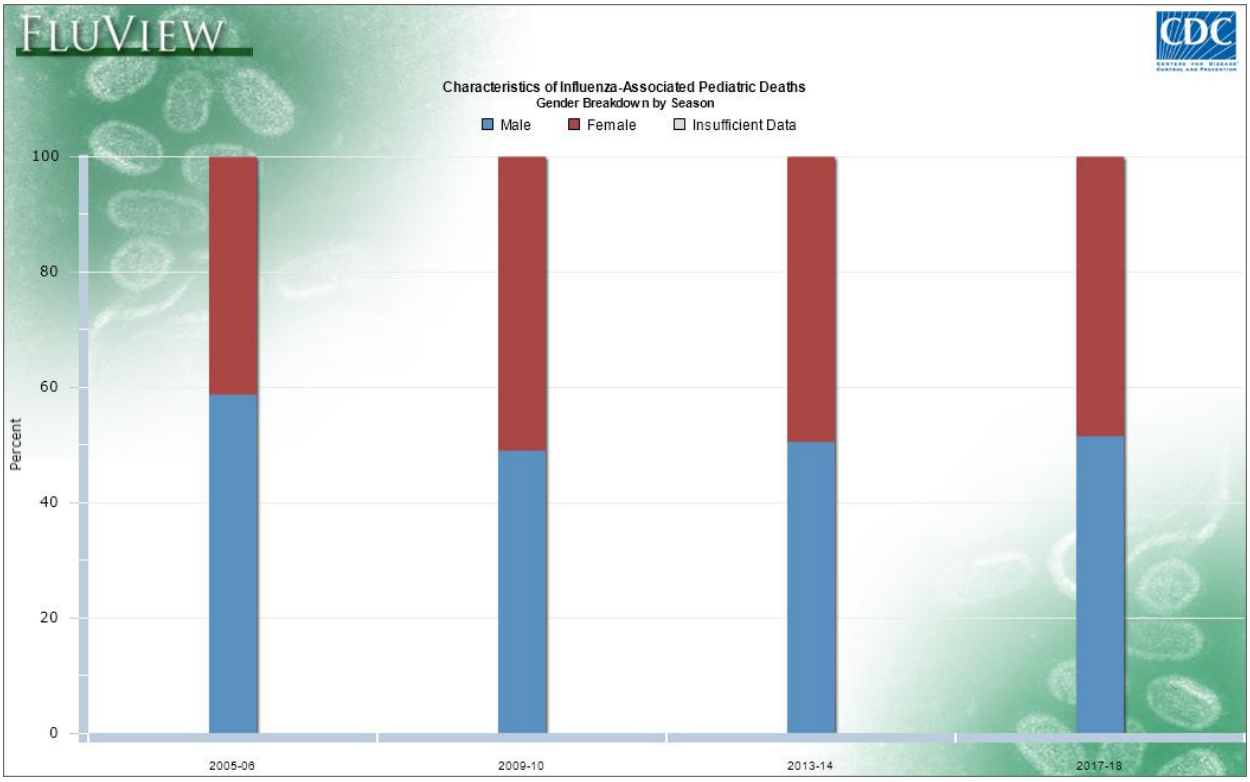


Figure 46. Death Rate by Gender

The 2005-2006 season shows slightly higher death rates for males, but the numbers are still well within the range of what would be considered equal risk for both sexes.

Figure 47, shows the number of confirmed hospital cases with the influenza A (Red) virus and the influenza B (Green) virus.

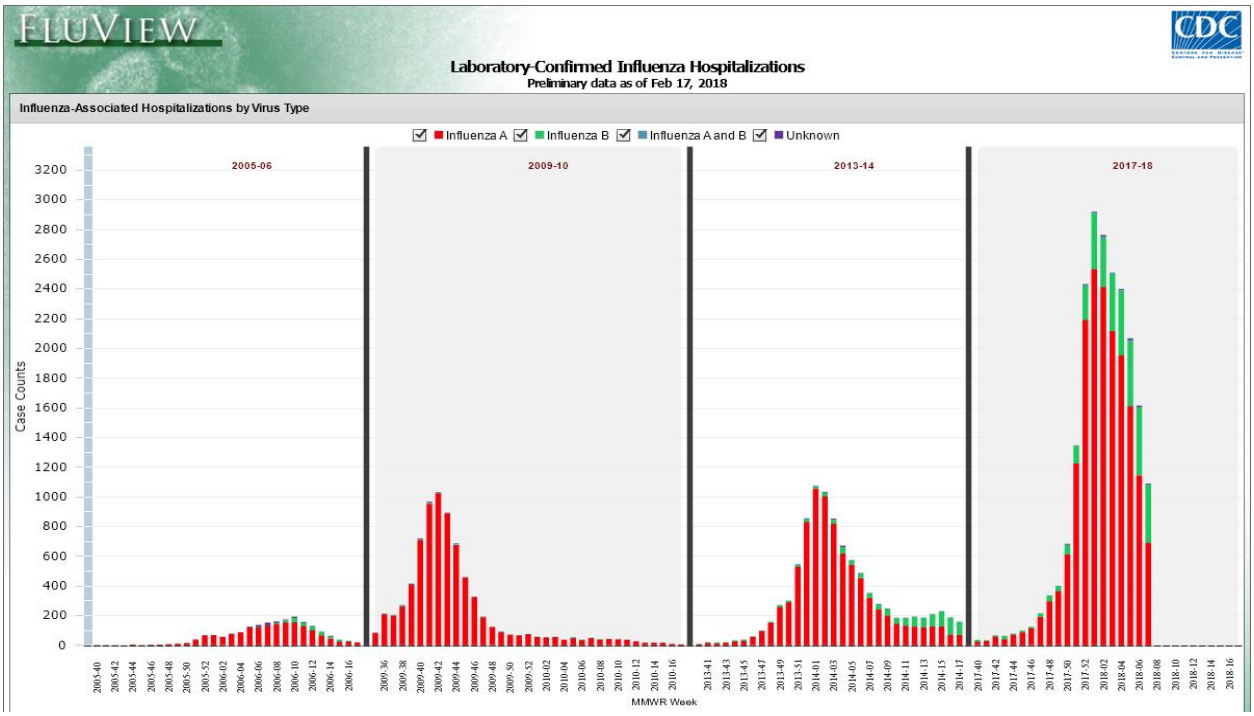


Figure 47. Confirmed Hospital Infections by Week

These seasons are consistent with the ones described above. An interesting fact that is brought to light by comparing these graphs, is the number of deaths recorded in the 2009-2010 season is significantly higher than the present season, due to the pandemic that was taking place in 2009. This graph, however, shows that the number of confirmed influenza cases is much lower in 2009, as compared to 2018. This indicates that the influenza virus this year is infecting more people, but is far less deadly than the 2009 H1N1 strain. The age breakdown of confirmed hospital cases is also consistent with expected results.

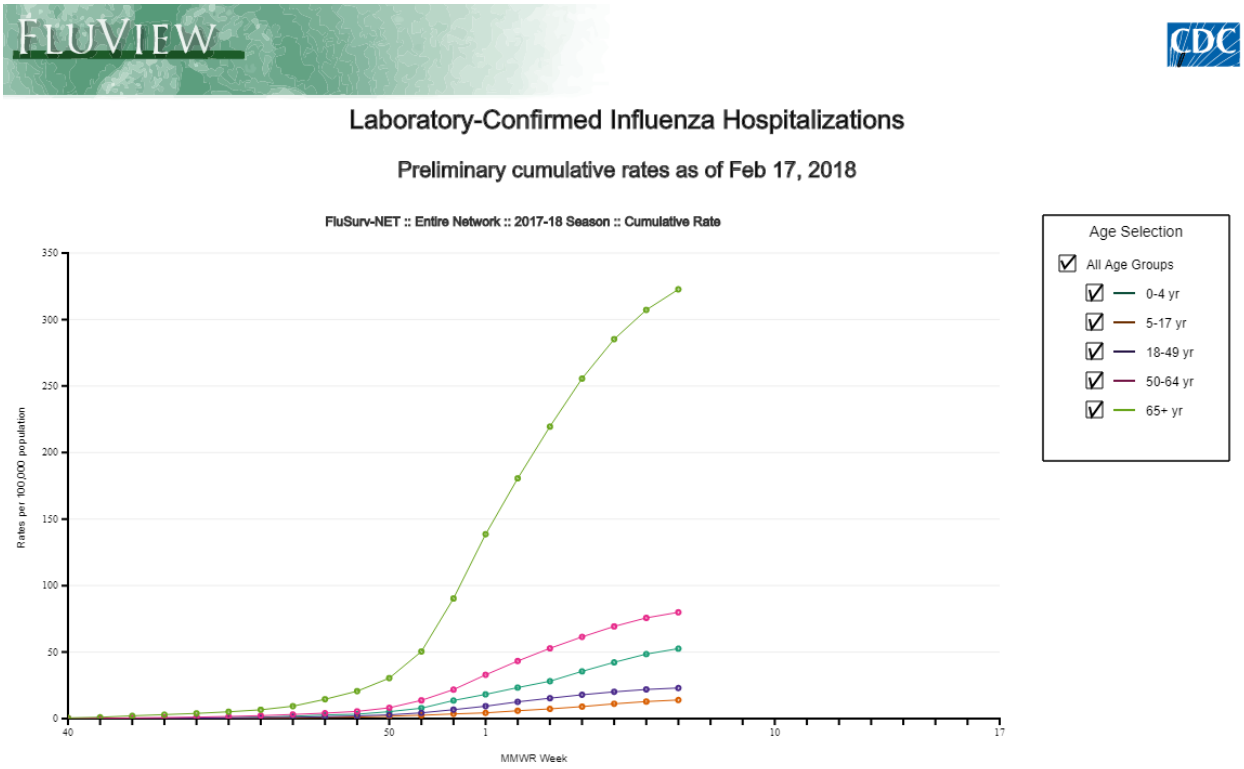


Figure 48. Age Group Breakdown of Current Influenza Hospitalizations

As we can see in Figure 48, the elderly population, over the age of 65 is at a significantly higher risk of being infected and hospitalized with the influenza virus.

3.2.3. Protecting At-risk Populations

Vulnerable and at-risk populations are important to consider in the context of influenza, especially with respect to pandemic outbreaks. Considerations for such patient populations is critical as inadequate preparedness to respond to outbreaks in these populations could lead to increased risk and transmission to the general population (Hutchins, 2009). The US response to Pandemic Influenza is outlined in the US National Strategy for Pandemic Influenza. Tenets of the strategy are structured among the objectives of stopping, slowing, or limiting the spread of the pandemic, limiting the domestic spread and mitigating disease, and finally maintaining

infrastructure and mitigating the impact to the economy and society as a whole (Homeland Security Council, 2007). In accordance with the first tenet of the US National Strategy for Pandemic Influenza, limiting spread can be addressed by providing prevention and control measures to high-risk populations. Adequately defining high-risk patient populations are required in order to appropriately identify where prevention resources are required. Health vulnerability and patient disease risk are the major factors in identifying such high-risk populations.

Table 6. NRF and DHHS Definition of At-Risk Individuals

Functional Area	Definition
Independence	individuals in need of support that enables them to be independent in daily activities
Communication	individuals who have limitations that interfere with the receipt of and response to information;
Supervision	individuals who require the support of caregivers, family, or friends, or have limited ability to cope in a new environment
Transportation	individuals who cannot drive because of the presence of a disability or the absence of a vehicle
Medical Care	individuals who are not self-sufficient or do not have adequate support from caregivers and need assistance with managing medical conditions

Health vulnerability is classified among socioeconomic and community-level factors that contribute to an individual's lack of resources to protect their health (Shi, 2005). Public health considerations for determining an individual's risk related to particular disease is the probability of developing the disease in a specific time interval (Hutchins, 2009). At-risk populations have been defined as children, pregnant women, senior citizens, and others who have special needs in a public health emergency, according to the December 2006 Pandemic All-Hazards Preparedness Act (Hutchins, 2009).

The National Response Framework (NRF) expands the consideration of individuals who require special needs in public health emergencies as outlined in Table 6 (HHS, 2007, NRF, 2008). Understanding patient demographics to appropriately allocate pandemic prevention resources allows efforts to combat the outbreak to be most effective.

Preparedness, including special considerations for high-risk/ vulnerable populations, has been suggested as a major component of any potentially successful pandemic response plan. Recognizing that vulnerability is not a function of poverty alone (Hutchins, 2009) as identifying potential cultural and racial/ethnic barriers are important to protection of these populations. From these considerations, it is inherently important to understand that lines of communication need to be established between public health agencies and identified vulnerable populations (Hutchins, 2009).

3.3. Prevention Measures

In order to prevent influenza, multiple basic steps should be taken. These range from maintaining basic hygiene to getting yearly inoculation against the flu. Though these measures are effective, with vaccination reducing ICU admission by up to 63% (Arriola et al, 2017), many of these preemptive interventions need to be done by the general population. Reminders and background information should be available to everyone in order to ensure maximum coverage. There are slight differences in how this information may be provided, depending on the target audience, whether they be the public, students, or healthcare providers.

3.3.1. Centers for Disease Control and Prevention (CDC)

Prevention of influenza requires cooperation of the public. The general populace must be informed of proper hygiene and steps which they can take to personally avoid contracting the flu and they must follow them. In the public sector, this can be accomplished through advertisement over television or radio, or through the older method of posters. The CDC currently runs a line of posters outlining basic hygiene to avoid spreading disease titled "Cover Your Cough" (Figure 49; CDC "Cover", 2015) with different variations depending on the audience.

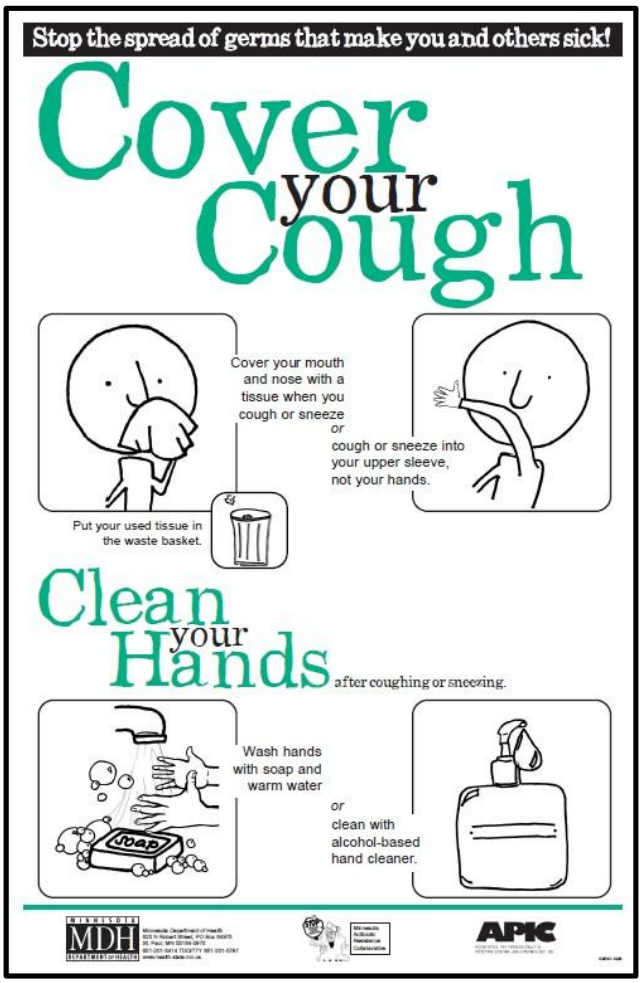


Figure 49. CDC "Cover Your Cough" Poster for Community and Public Settings

These posters, designed by the Minnesota Department of Health, outline basic hygienic practices which anyone may follow. The information is displayed in short phrases available in 26

languages, with simple pictures so anyone may understand and has been circulating for over 6 years at the time of writing (2018) (CDC “Respiratory”, 2012).

3.3.2. Hospital

Prevention of influenza does not only take place in the general public, but must also take place in the hospital. It is important for facilities in the healthcare setting to take precautions against the flu. Since healthcare professionals should, if sick, be avoiding contact with patients, emphasis should be placed on sanitation of the hospital or clinic. Sani-cloths (Figure 50; PDI, 2018) and other disinfectant wipes should be used to clean surfaces which patients or providers may come into contact with. These wipes have been proven to kill several pathogens including influenza, when used on hard non-porous surfaces.

Figure 50. Super Sani-Cloth

Reminders for providers to wash their hands in between patient interactions should be posted to keep direct contact to the provider and indirect contact to other patients at a minimum (Figure 50). These steps, in conjunction with utilizing RIDT’s in hospital triage, can lower the chances of spreading influenza from infected patients receiving treatment to uninfected individuals in healthcare settings.

3.3.3. Local Communities and Campuses

When applied to local communities and campuses, such as a college, for instance, the potential for more public exposure is possible. Most colleges have an email system which can be used to send out announcements and reminders for events on campus. This system could be used to send a public service announcement to the students, providing basic information on the flu and informing them how to avoid the disease. Community outreach coupled with vaccine availability at campus health services and publicly displayed posters, such as the ones provided by the Residential Services of Worcester Polytechnic Institute (WPI) (Figure 51), could mitigate spread of influenza across the campus.

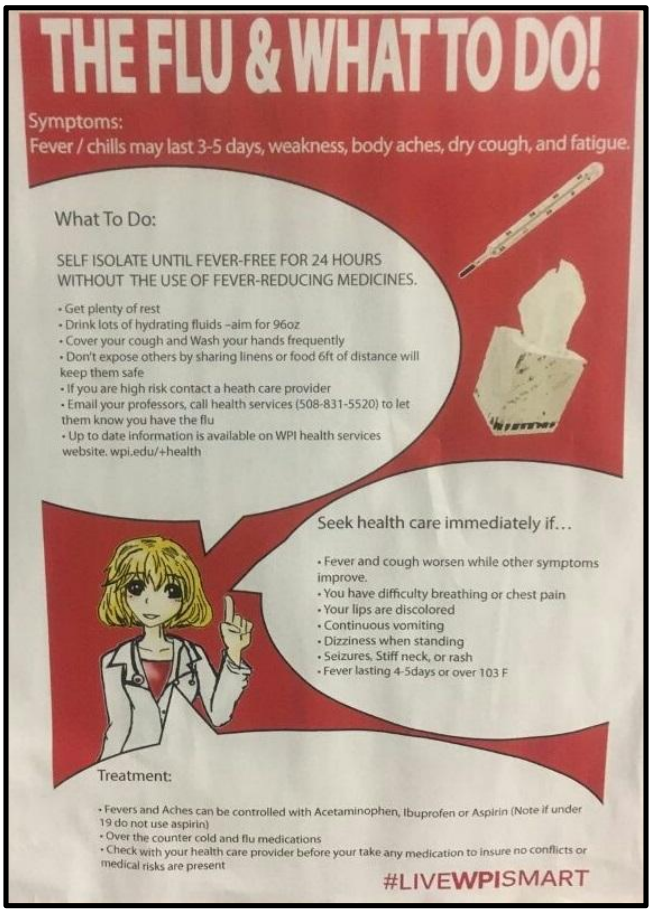


Figure 51. WPI "The Flu & What to Do" Poster

Another approach to public outreach could manifest in an application for smart devices, which could analyze the current risk of contracting influenza and provide warnings together with preventative measures to take. This could be noninvasive until the risk increases, helping to improve public vigilance concerning influenza.

3.4. Diagnosing Influenza

Influenza diagnosis is process that must be approached systematically to ensure physicians are correctly and accurately diagnosing patients. Physicians must first build a differential diagnosis based on patient symptoms. Combining symptoms with physical findings such as patient temperature (fever) can prompt physicians to order influenza tests. These tests require obtaining patient samples using nasal swabs. These samples can then be tested using molecular methods such as the *Alere i* device. Devices such as the *Alere i* utilize molecular biology to test for influenza.

3.4.1. Current Diagnostic Methods

Influenza diagnosis begins with obtain the patient's list of symptoms and their temperature. When a patient presents with "flu like" symptoms such as those listed previously, physicians suspect the flu. The presence of a fever is also a stronger indicator of whether a patient may or may not have the flu. Accurate thermometers such as that pictured in Figure 52, are frequently used in hospitals to obtain patient temperature to test for a fever.

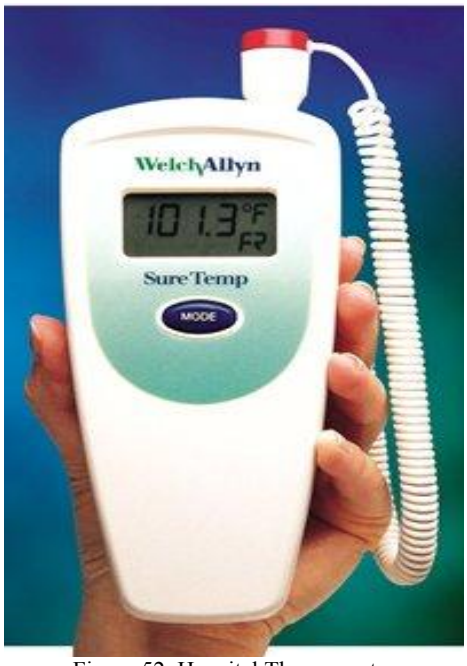


Figure 52. Hospital Thermometer

Patients suspected of the flu are tested to confirm the diagnosis. Prior to testing, a patient sample must be obtained. Patient samples are obtained using a sterile nasal swab shown in Figure 53. These swabs are kept in a sealed wrapper to maintain sterility.

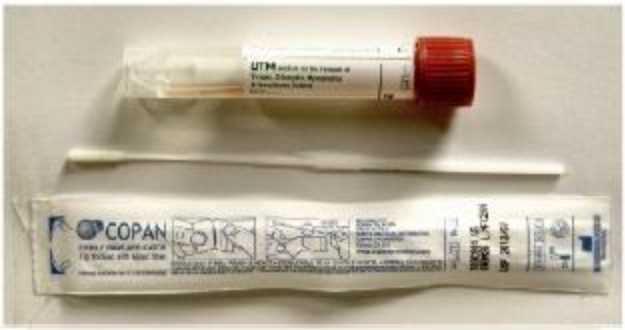


Figure 53. Influenza Nasal Swab

To ensure proper collection, trained professionals must always carry out the collection. As discussed previously, the virus attaches to the nasopharynx or the back of the throat. Figure 54 shows how to collect a patient sample. To ensure that an adequate sample is collected, the swap must go through the nose and touch the back of the nose where the virus is most abundant.

It is important to note that the health professional in Figure 54 is wearing proper Personal Protective Equipment (PPE) such as gloves and a gown for their protection and the protection of the patient.

Figure 54. Proper Nasal Swab Collection

Post collection, patient samples are can be tested in several ways. The Alere i system utilizes a molecular approach to test samples. This approach is discussed in the following section.

3.4.2. Rapid Testing Using Molecular Biology

The rapid testing technologies, such as *Alere i* utilize a molecular approach to the diagnosis of influenza. As previously discussed in Figure 53, patient samples are inserted into the sample receiver where the influenza particles are released into a buffer of specific solutions. These solutions are specifically designed to do several things. First, the solution must lysis or break open the virus to release the viral RNA (see Figure 55). Once the viral RNA is released into the solution, the test base begins to heat up.

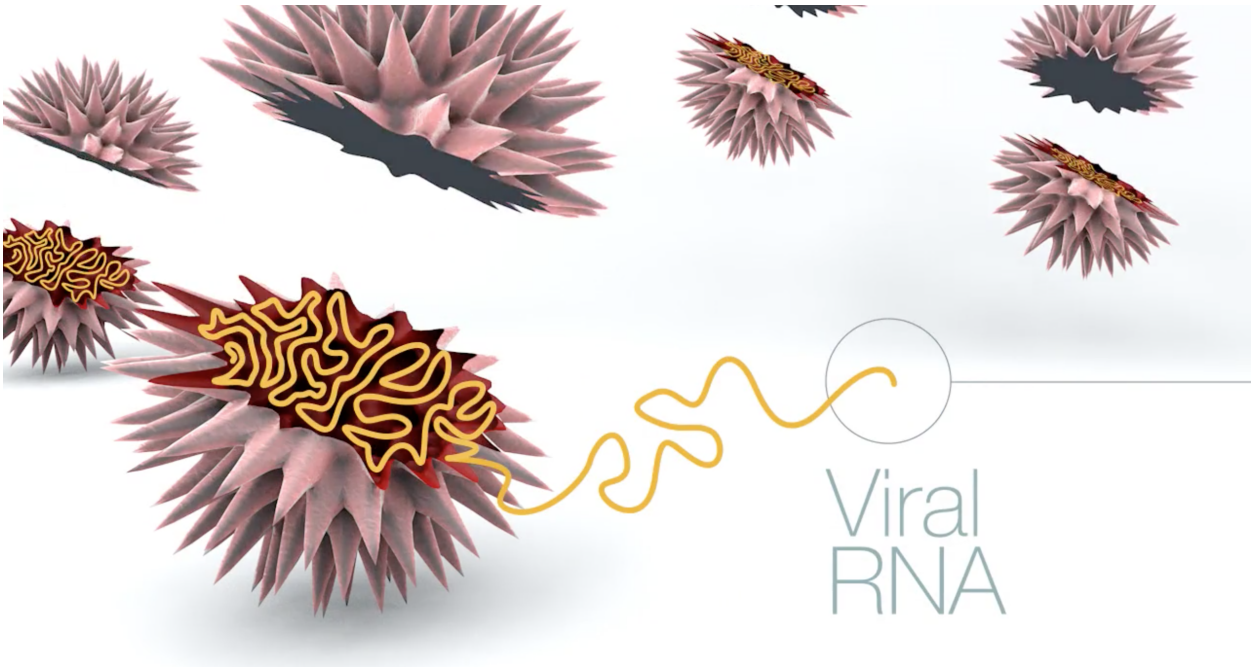


Figure 55. Viral RNA is Released into the Test Cartridge

Unlike conventional testing methods such as RT-PCR, *Alere i* does not need to cycle its temperature (see Figure 56). Instead, *Alere i* heats up to a little over 40°C and maintains this temperature. The system does so in approximately 3 minutes which allows for results to be populated in 15 minutes.

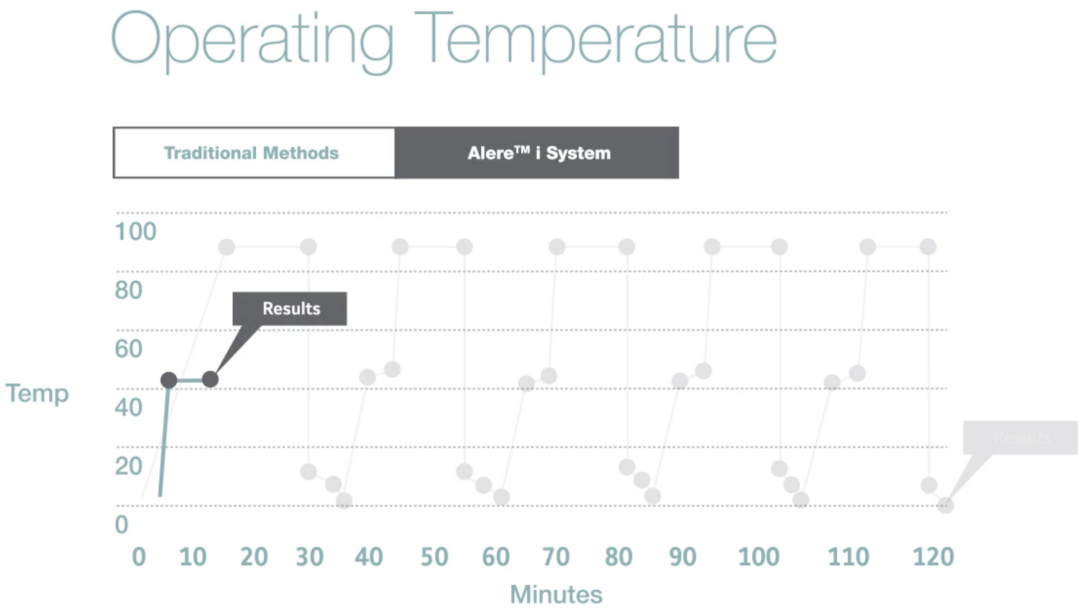


Figure 56. Alere i Works at a Constant Temperature

The next step is to make sure reagents in *Alere i* solution do not mistakenly give false negative or false positive results. This is in part due to the specificity of the reagents in *Alere i* solution. The solution contains specific RNA sequences that are only specific for either influenza A or B. in solution, these sequences find and attach to the target pathogen or target influenza sequence (see Figure 57).

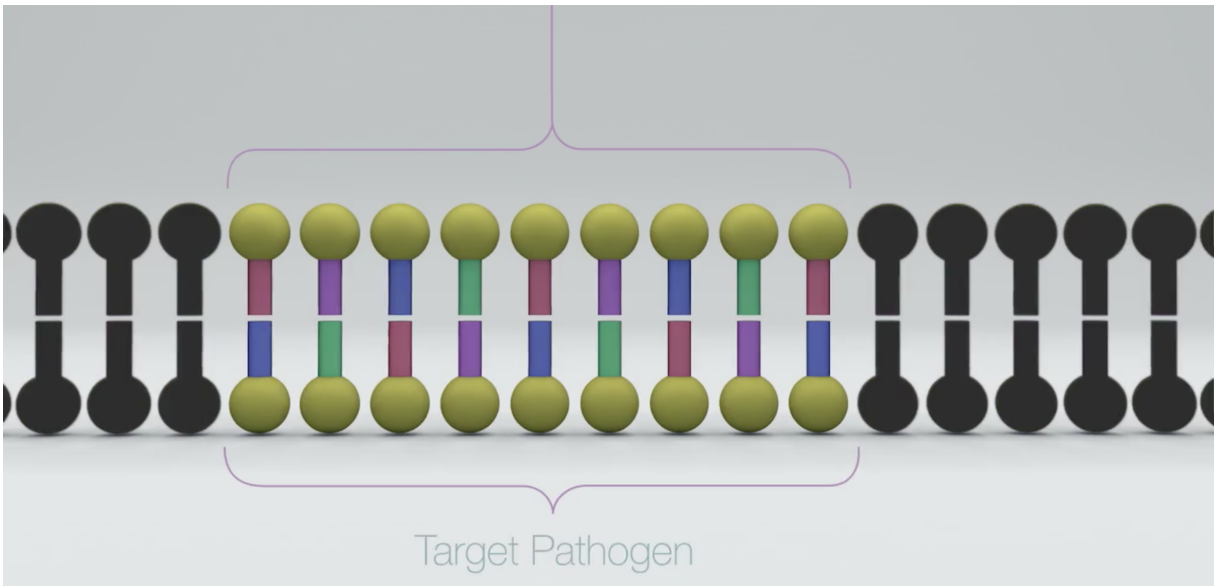


Figure 57. Targeting Influenza Specific Sequences

After a specific sequence is found and targeted, replication is necessary to produce enough of this sequence for a positive test result. In the solution are fluorescent labelled nucleic acids, termed fluorescent probes. During target viral RNA replication, these probes are incorporated in the newly synthesized sequences (see Figure 58).

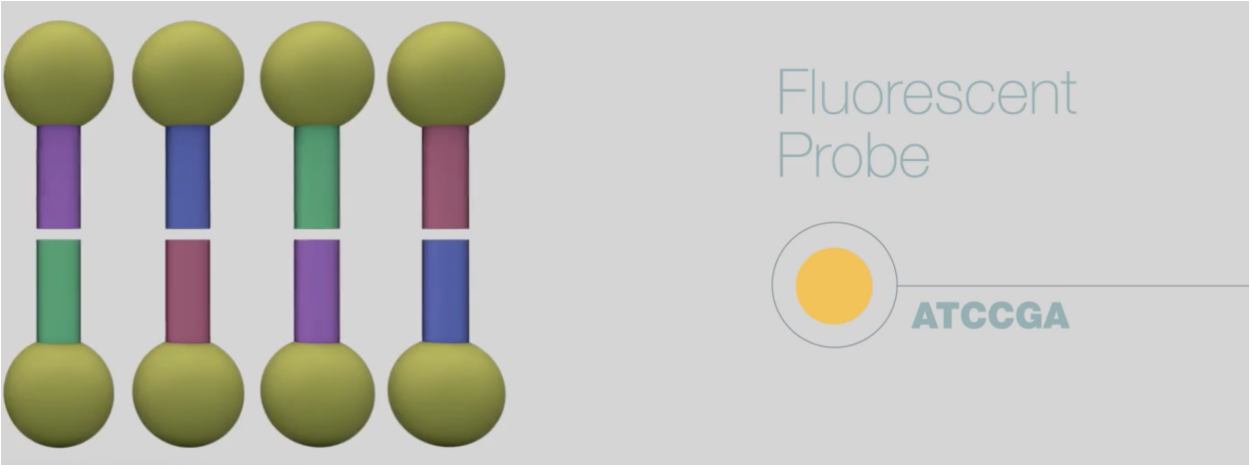


Figure 58. Fluorescent Probes Mark Target Viral RNA

As more replication events take place, the fluorescence of the sample increases. At a certain threshold determined by the device, the program determines that there's now enough fluorescence to positively say that the patient sample tested is influenza positive. In the same way, if the fluorescence threshold is never reached then the program can determine that the patient sample inserted is influenza negative.

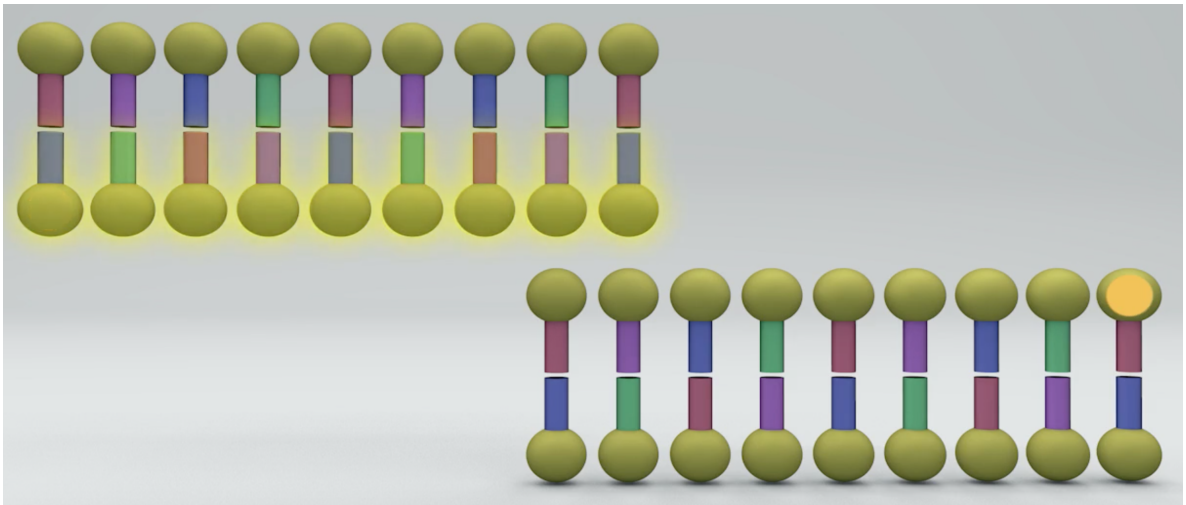


Figure 59. Fluorescence as a Positive Test Marker

The total elapsed time from patient sample insertion to results is approximately 15 minutes. At the end of this time, *Alere i* software is able to tell the user two important piece of

information. First, the fluorescence probes enable the software to determine if the patient sample is positive or negative for influenza regardless of the type Second, thanks to the sequence specificity of *Alere i* reagents, it is able to determine if the patient is influenza A or B positive. All of this information is then displayed to the user on the screen, can be printed, and can also be electronically sent to the patient's medical record.

3.4.3. Benefits of Rapid Testing

Novel identification of influenza and improved diagnostic capabilities are currently available through Point of Care (POC) Rapid Influenza Diagnostic Tests (RIDT). The ability to rapidly and accurately diagnosis influenza in patients has the capacity to positively influence management of a patient's illness. Management decisions such as decreased antibiotic usage, improved criteria for the appropriate administration of antiviral therapies and large reduction in time spent in emergency department have all been determined to be associated with RIDT POC implementation (Hurt, 2007).

Randomized prospective studies have been designed to determine the decision-making influence that positive rapid influenza test results have on physician decision making (Bonner, 2003). Patients between the ages 2 months and 21 years, presenting as febrile with a temperature of 100.4 F or greater, coupled with an additional influenza like illness "ILI" (cough, coryza, malaise, headache, myalgias) and an onset of symptoms within 72 hours were included in this particular study. Over the duration of 46 days, 418 patients were studied. One group had their care managed by a physician who did not receive the test results while the other group's physician was aware of the rapid influenza diagnostic test result. The findings of this study revealed that physicians aware of the test results dramatically altered patient care management and decision making. These decisions were embodied as decreased antibiotic use, increased

antiviral use and decreased length of stay in the ED (Bonner, 2003). The specific findings are shown in Table 7 (Bonner, 2003).

Table 7. Tests Performed, Associated Charges, Prescriptions, and Time to Discharge

	MD Aware of Positive	P-Value	MD Unaware of Positive	MD Aware of Negative	MD Unaware of Negative	P-Value
Sample Size(n= 391)	n= 96		n= 106	n=97	n=92	
Complete Blood Count	0	<.001	13	13	7	0.196
Blood Culture	0	<.001	11	12	6	0.172
Urine Dipstick	4	0.543	7	7	7	0.918
Urinalysis	2	0.011	12	10	8	0.706
Urine Culture	3	0.011	14	12	5	0.096
CSF Studies/Culture	0	0.499	2	3	2	0.695
Chest Radiograph	7	0.001	26	22	23	0.708
Mean charge/ patient (lab and radiograph)	$15.65	<.001	$92.37	$93.07	$68.91	0.871
Antibiotic Prescriptions	7	<.001	26	27	27	0.818
Antiviral Prescriptions	18	0.02	7	0	2	0.236
Mean time in minutes (from patient examined by attending to discharge)	25	<.001	49	45	42	0.549

From Table 7 it is easy to recognized that additional tests are reduced in addition to cost and time spent in ED when there is a positive test result and the physician is aware of it. These differences in tests, costs and time are all calculated to be of statistically significant difference within this study in regards to their small calculated P-Value.

It is important to consider the demographics of the associated test group as divided among the adult and pediatric cohorts in this prospective study. This is directly related to the viral pathogenicity varying in age groups. Particularly in pediatric patients due to the higher rate of viral shedding for longer periods than adults who have more developed immune systems the RIDT POC tests typically reveal higher sensitivity and specificity for pediatrics (Upton, 2006).

An additional randomized prospective study conducted at the Vanderbilt Pediatric Emergency Department over two consecutive flu seasons provides additional insight on the effectiveness of the QuickVue influenza test (Poehling, 2006). Table 8 (Poehling, 2006) shows the impact that the rapid test had on subsequent tests completed on the pediatric patients under that age of 5 in the emergency department.

Findings from this study overall indicated a 12.5% overall reduction in unnecessary diagnostic testing for pediatric patients with respiratory symptoms (Poehling, 2006).

The researchers of this study concluded from the data that confirming the diagnosis of influenza could function as the major role POC RIDT could serve in the ED. In this regard it has potential utility as being able to benefit patients 12 months of age or older presenting in the ED within the time frame of 1 or 2 days of symptom onset. This criteria would establish the patients as a candidate for antiviral medication and optimize treatment of the patient's condition. The implementation of such testing devices effectively serves to eliminate the question of additional causes of a patient's presenting illness by providing a clear and actionable diagnosis, to which healthcare providers can respond.

Determining the specific cause of pediatrics presenting with fever and vague symptoms reduces concern that the patient is suffering from unknown life threatening conditions. By ruling out the presence of influenza it subsequently decreases the necessity of further tests such as blood counts/cultures, urinalysis, lumbar punctures and radiographs. Rapid and accurate diagnosis of the illness establishes an actionable widow to manage influenza patients with antiviral therapies of oseltamivir (McLean, 2015), zanamivir (Hayden, 1997) amantadine and rimantadine. The efficacy of these drugs have indicated that the appropriate administration of these antiviral medications can advance illness resolution when compared to non-treated groups and placebos (CDC, 1999, Aoki, 2012).

Table 8. Impact of Rapid Test on Diagnostic Testing in the Emergency Department

Diagnostic Test:	Rapid Test	No Rapid Test	P-Value	Rapid Test	No Rapid Test	P-Value
	Overall			Influenza Positive		
Sample Size:	n= 135	n= 170		n=28	n=29	
Any Diagnostic Test						
Yes	53 (39)	88 (52)	0.03	9 (32)	12 (41)	0.47
No	82 (61)	82 (48)		19 (68)	17 (59)	
Chest Radiograph						
Yes	31 (23)	56 (33)	0.06	3 (11)	7 (24)	0.18
No	104 (77)	114 (67)		25 (89)	22 (76)	
Blood Count/Culture						
Yes	14 (10)	31 (18)	0.05	1 (4)	3 (10)	0.61
No	121 (90)	13 9(82)		27 (96)	26 (90)	
Urinalysis/Culture						
Yes	18 (13)	27 (16)	0.53	3 (11)	3 (10)	1
No	117 (87)	143 (84)		25 (89)	26 (90)	
Antibiotics						
Yes	43 (32)	49 (29)	0.57	4 (14)	5 (17)	1
No	92 (68)	121 (71)		24 (86)	24 (83)	
Antivirals						
Yes	1 (1)	0	0.44	1 (4)	0	0.49
No	134 (99)	170 (100)		27 (96)	29 (100)	

Table 8 provides an overview of the antiviral medication methods and criteria for their respective application. The relation of these drugs and early detection are related primarily through the criteria that diagnosis within 36-48 hours of symptom onset (Aoki, 2012). Otherwise they are typically contraindicated on behalf of them being largely ineffective. Therefore, by implementing early detection, patients have an increased chance of being diagnosed in a time frame complementary to the antiviral medication administration criteria.

The efficacy has been demonstrated in these antiviral medications through reduction in disease progression in patients with uncomplicated, self-limited, laboratory-confirmed influenza (Aoki, 2012) (see Table 9; CDC, 1999).

Table 9. Applications of Influenza A and B antiviral Therapies

	Amantadine	Rimatantadin	Zanamivir	Oseltamivir
Types of influenza viruses inhibited	influenza A	influenza B	influenza A and B	influenza A and B
Route of administration	Oral (tablet, capsule, syrup)	Oral (tablet, syrup)	Oral Inhalation	Oral (capsule)
Ages for which treatment is approved	>= 1 year	>= 14 years	>= 12 years	>= 18 years
Ages for which prophylaxis is approved	>= 1 year	>= 1 year	Not approved for prophylaxis	Not approved for prophylaxis

The significance of identifying age groups and criteria that benefit most from POC RIDT implementation is important especially when pediatric cohorts are compared to High-Risk adults. The cost effectiveness appears to also change when the healthcare setting is characterized between outpatient clinics and Emergency Departments. Research through the University of South Carolina School of Medicine has revealed that rapid testing is the most cost-beneficial approach when clinicians intend to prescribe non-neuraminidase inhibitors for treatment instead of the more expensive neuraminidase inhibitors (Hueston, 2004). The respective costs of each antiviral medication in addition to other cost assumptions considered in this study are presented in Table 10 (Trabattoni, 2017). The other assumptions made is that the patients who are unvaccinated and within the demographics for the study are reporting to the clinician within 48 hours of symptom onset.

Table 10. Baseline Probability & Cost for influenza: Testing-Treatment Model

Variable	Baseline Assumption	Sensitivity Test Range
Cost assumptions		
Cost of diagnostic test, $	20	5–30
Benefits of recovery, $	177.2	*
Additional physician visit for drug reaction, $	40.48	32.38–48.54
Complication with hospitalization, $	8,960.20	7,175–10,763
Medication costs (full course of therapy)		
Amantadine, $	10.5	8.40–12.60
Rimantadine, $	24.08	19.26–28.90
Zanamivir, $	49.35	39.48–59.22
Oseltamivir, $	61	48.80–73.20
Probability assumptions		
Test sensitivity, %	72.5	50–95
Test specificity, %	90	80–00
Probability of drug side effect, %	3	0–6
Probability of influenza complication, %	0.5	0.3–5

All the patients included in the study were over 65 years old and those over 50 with a diagnosis of chronic respiratory tract conditions (COPD or asthma) or diabetes or cardiac history. The decision making process for the study was divided among three treatment strategies. These strategies considered no treatment, Empirical treatment and test-treatment. Both no-treatment and the empirical treatment strategies were further divided into low-risk and high-risk patient groups. The overall cost reduction was demonstrated in the empirical treatment strategy. Within this treatment method the low risk cohort demonstrated the largest cost reduction. These findings were arrived at on the basis that the test is not required and treatment is still provided. Within the empirical treatment strategy influenza testing is only cost-beneficial when the patients possess an elevated risk of complications (Hueston, 2004).

Cost-benefit of these measures were measured by metrics of lost productivity due to flu progression. Additionally human capital is considered in measures of incremental costs

associated with influenza progression, cost of treatment and diagnosis. Such variables affected are direct medical costs, indirect cost of lost wages due to loss of productivity and insurance costs. Complication costs were Figured from the mean cost of hospitalization due to influenza (Hueston, 2004). The breakdown of the effectiveness among the three treatment strategies in relation to specific antiviral medications are depicted in Table 11 (Hueston, 2004). Although the findings from this study reveal that test-treatment strategy is not universally cost reductive it does provide insight as to how RIDT could lead to informed decision making in relation to antiviral drug administration. Another consideration made from interpreting this study is determining the most effective health care setting to implement such RIDT devices.

Table 11. Most Cost-Beneficial Treatment Strategy for Each Antiviral Drug

Drug Prescribed	No Treatment %	Test Before Treatment %	Empirical Treatment %
Amantadine	<5	--	≥5
Rimantadine	<11	--	≥11
Zanamivir	<19	≥19 but ≤28	>28
Oseltamivir	<22	≥22 but ≤36	>36

The research studies previously mentioned and the ability to synchronize diagnosis within a complementary time frame of antiviral drug administration provide evidence in support of early detection RIDTs to address influenza. Applications of POC RIDT devices have been revealed to have potential cost reduction in numerous patient age groups. Focusing on specific devices such as the *Alere i* influenza A&B allows a more in-depth glance at the potential cost reduction and improved care that can be provided to patients presenting with symptoms of influenza. There have been numerous studies conducted to reveal that the *Alere i* is capable of achieving reduction in the metrics mentioned above while also providing a level of sensitivity and specificity competitive with the previous standard of care RT-PCR influenza tests.

Research has been completed on implementation of the *Alere i* influenza A&B in the Emergency Department at Groupe Hospitalier Paris Saint-Joseph in Paris, France. The findings revealed that the *Alere i* device has the ability to reduce the length of stay in the ED, hospitalization rate and the number of additional tests (Trabattoni, 2017). In this study the *Alere i* A&B using direct nasal swabs was used to test adult patients presenting with ILI symptoms. The standard of care lab based PCR results was used to confirm the diagnostic findings. The specific findings within the study are included in Table 12 (Trabattoni, 2017). Major overall findings reveal that POCT has the potential to increase ED efficiency by reducing mean time spent in ED and requirements for additional tests. Unlike findings from previous studies mentioned the results of this study demonstrated similar rates of both antibiotic and antiviral therapies (Trabattoni, 2017).

Table 12. Diagnostic Time and Treatment Data

Diagnostic Data	Pe POCT N = 169	POCT N = 132	P value
Patients tested for influenza, n (%)	25 (14.8)	132 (100)	–
Patients with positive test result, n (%)	9 (5.3)	41 (31)	<0.01
Mean age of patients with positive result (95% CI)	35.9 (23.7–53)	38.7 (31–49)	0.97
Time spent in ER (h) with positive Flu test mean (IQR)	6 h06 (±3 h01)	4 h15 (±2 h32)	0.03
Antibiotic prescription, n (%)	60 (35.5)	39 (29.5)	0.32
Antiviral prescription, n (%)	4 (2.4)	7 (5.3)	0.22
Chest X-ray, n (%)	132 (78.1)	82 (62.1)	0.003
Biochemical/hematological tests	136 (80.5)	84 (63.6)	0.001
Urinary antigens			
Legionella pneumophila	21 (12.4)	14 (10.6)	0.71
Streptococcus pneumoniae	21 (12.4)	12 (9)	0.45

Multicenter clinical evaluations have been completed on the *Alere i* A&B influenza test and have revealed that the *Alere i* influenza has sensitivity and specificity for influenza A 99.3% and 98.1%, and influenza B 97.6% and 100% respectively (Bell, 2014). It also demonstrates a faster turnaround time than lab based viral culture or RT-PCR tests. The studies described provide metrics and criteria that support the efficiency of using the *Alere i* A&B in both the healthcare clinic and Emergency Department settings.

3.5 Conclusion

Influenza poses a substantial health risk to the human population. The nature of the virus causes it to resurface on a yearly basis. In rare cases, a particular year will be hard hit and the virus will spread around the globe, in what becomes known as a pandemic. The data and graphs from the CDC illustrate these yearly occurrences of the virus' infection and mortality rate. Based on these values, we are able to see the groups of individuals who are more at susceptible to the virus. We are also able to track the conditions surrounding an outbreak in a given year and hypothesis toward a permanent solution.

Through the application of this data and data from similar sources, the CDC defines methods of limiting the virus' spread. We have shown that the virus is transmitted through person to person contact, through person to infected object contact, as well as, through airborne droplets. Following recommended sanitary habits help limit the spread of the flu in all three of these transmission areas. For individuals, the CDC recommends proper hand washing, avoiding direct contact with infected individuals and restricting travel outside of a person's house when they are ill. To limit non-contact transmission, the CDC recommends cleaning and disinfecting

commonly touched surfaces often, as well as, regularly cleaning and disinfecting all surfaces. These practices allow for germs to be killed, thus causing the rate of infection to decrease.

These practices, however, need to be coupled with proper medical training and technology. The CDC's information on proper sanitary measures also fail to help those who are unaware of its existence. Reminders for providers to wash their hands in between patient interactions should be posted to keep direct contact to the provider and indirect contact to other patients at a minimum (Figure 43). These steps, in conjunction with utilizing RIDT's in hospital triage, can lower the chances of spreading influenza from infected patients receiving treatment to uninfected individuals in healthcare settings.

Chapter 4. Conclusion

Influenza is one of the most-deadly viruses in the history of humankind. Throughout the 20th and 21th Centuries, influenza pandemics have had a substantial adverse impact on the way scientists and healthcare providers study, analyze, and contain the spread of infectious diseases. Historical evidence has shown that influenza is a threat through its ability to survive and thrive in most of the world's environments, thereby allowing it to trigger several global pandemics. The 1918 Spanish Flu, which killed more than 50 million people with a 2.5% mortality rate, is less deadly than other influenza strains. For instance the H5N1 strain, which possess the same degree of infectiousness, carries a documented death rate of over 40%.

Understanding the historical impact and context of influenza pandemics has provided a foundational understanding of various factors that contribute to the mortality rate, and provide insight on how to limit the spread of influenza. From literature review and study of historical events, three major modes of transmission can be identified and traced. These modes of transmission are composed of direct contact, indirect contact, and non-contact. Through the identification of the transmission modes, preventative measures can be effectively implemented to mitigate individual exposure to infectious viral agents. Understanding how influenza is transmitted between hosts allows medical professionals and scientists to develop novel preventative measures that are able to limit the spread of influenza and therefore limit the threat of the virus.

The spread of influenza is partly dependent on influenza seasonality. Scientists and healthcare professionals have provided several theories. As the influenza viruses continue to undergo genetic drift, there are more and more individuals, in particular those individuals with weak immune systems who are unable to recognize the new strains. Other research has focused on how the changing climate affects individuals' susceptibility to influenza, including changes in

vapor pressure and humidity. Some studies analyzed the effect of changing the behavioral patterns of influenza carrier in terms of exposure risk and vulnerability. The genetic drift theory is the theory most accepted by scientists, however other factors such as public health measures and early report of symptoms have shown to reduce the risk and vulnerability of influenza exposure.

In hospitals, sanitary rules include hand washing, constant sanitization of surfaces, and self-quarantining of suspected influenza carriers. Other guidelines focus on constant ventilation and filtration of air to remove any airborne virus particles. As a more active form of prevention, public health measures are implemented to slow the spread of influenza with a community. Every year across the United States, the number of vaccination centers are growing. Federal, State and Local Governments inform the population when and where to obtain vaccination. Vaccination is recommended by healthcare providers as an important preventive measure. Studies have shown that vaccination improve immune systems by allowing the host's immune system of influenza to recognize the virus and produce the appropriate antibodies. Other public health measures use containment rather than prevention. Suspected individuals with influenza are separated from healthy population or prohibited to travel in an effort to stop the influenza carrier from transmitting the virus to other communities. All of these measures have proven to be effective in limiting the spread of influenza and selecting treatment options for influenza carrier.

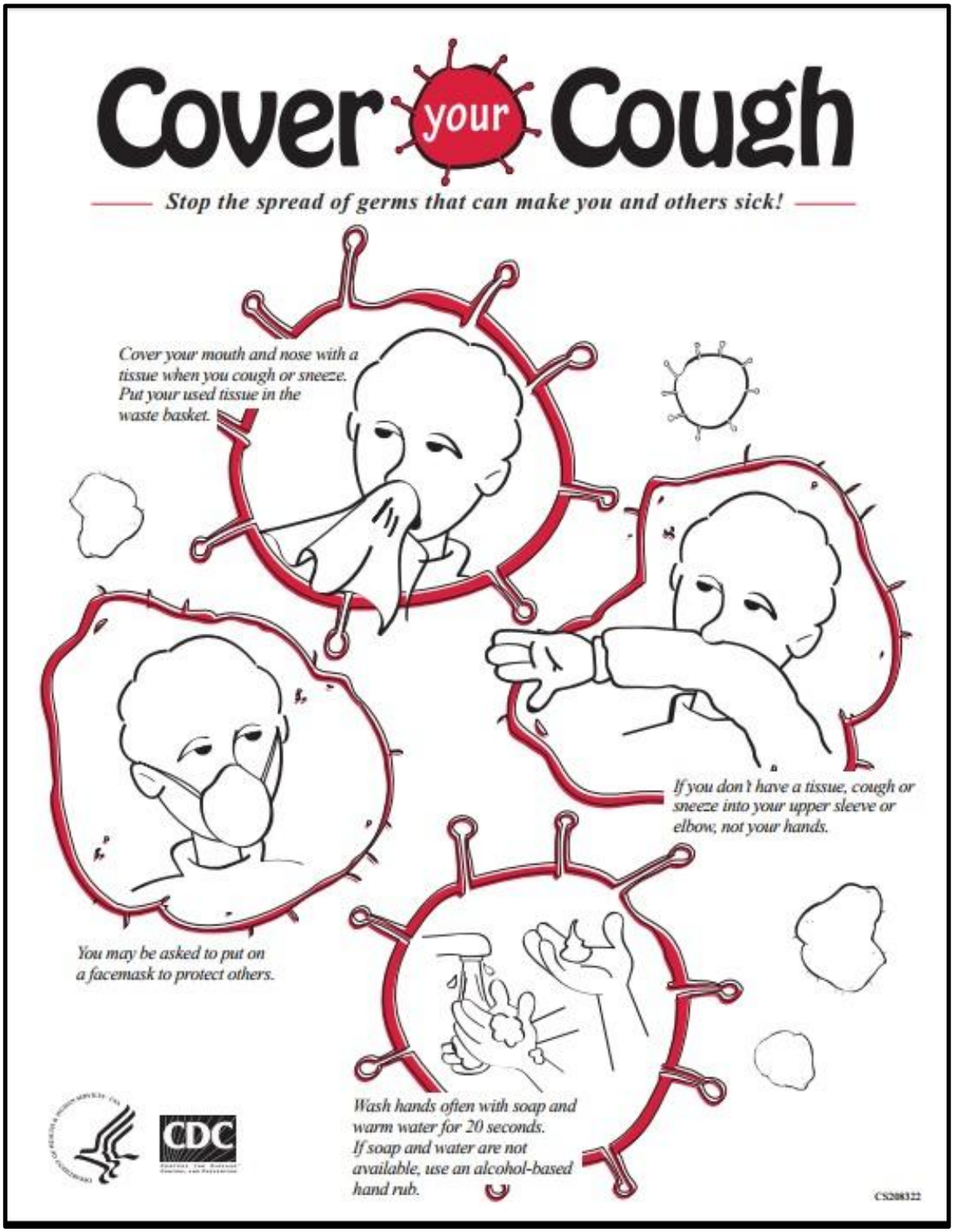
Diagnosing influenza can be difficult - many of its symptoms are similar to other diseases and often individuals just assume that they have a cold. In a home setting, patients can look for rapid flu-like symptoms including fever, coughing, and nasal congestion. In order to officially diagnose an individual with influenza, the patient must be evaluated by a medical professional. With today's technology, a laboratory using RT-PCR testing is able to diagnose an individual carrying influenza. Molecular testing, seen in platforms such as the Alere i system and other RT-

PCR systems now available in the molecular biology market, are capable of testing influenza carriers in a timely manner. Many hospitals, clinics and disease diagnostic centers use RT-PCRs for early detection of influenza and other infectious diseases. A more rapid diagnosis of influenza, combined with an understanding of the modes of transmission and preventive measures, may reduce the spread of influenza within communities. This could be as simple as having diagnosed individuals self-quarantine to avoid spreading influenza to uninfected populations such as colleagues, work places and mass gatherings. Taking such preventive measures, the number of infected individuals are reduced and the cost of treating influenza patients, as well as possible lost income by infected individuals are reduced. By implementing influenza rapid-testing across a wide scale, it would be possible to contain outbreaks before they become pandemics - an advantage that should not be underestimated.

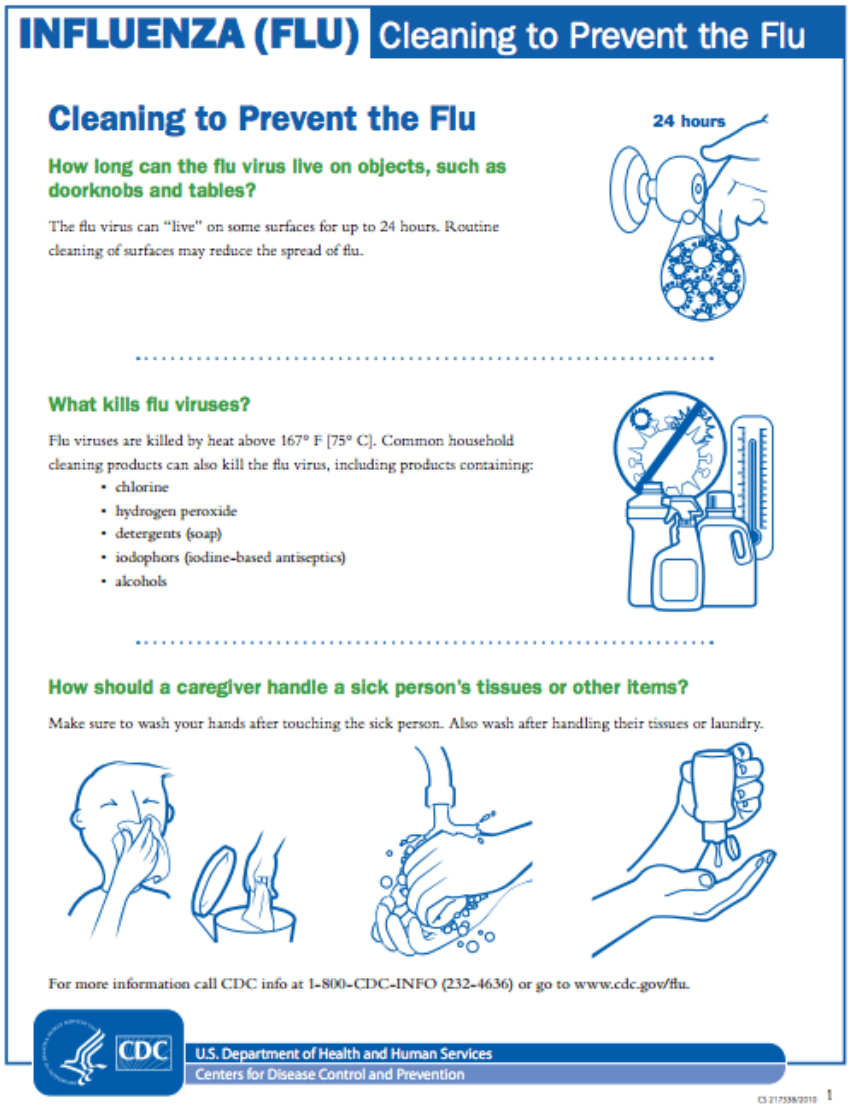
In order to facilitate the containment of influenza, this project has produced a website that informs the public about influenza The website contains an overview of the history of influenza, which covers the major influenza pandemics as well as the various lessons learned. The website also contains preventive measures and public health guidelines on limiting the spread of influenza from person to person. In addition, preventative and diagnosing methods are explained on the website. The last informational page contains treatment options of influenza and recovery process. Finally, the website contains an interactive map which users can look up the current state of influenza according to data collected by CDC. Each State of America has its own influenza level as well as some guidelines from CDC on how to protect oneself from influenza exposure. Visitors to this site will be able to learn the relevant information about influenza and treatment options. The homepage clearly links to the subpages, each of which is detailed yet not overly complicated. By making the website accessible to everyone with internet services,

describes the social impact of the Interactive Qualifying Project on developing influenza disease solutions.

Appendix



Appendix 1. CDC "Cover Your Cough" Flyer for Health Care Settings (CDC "Cover", 2015)



Appendix 2. Cleaning to Prevent the Flu ("Contamination Cleaning" CDC, 2010)

Appendix 3. CDC Poster 1963 (CDC “Wellbee”, 1963)

References

Abanses, J. C., Dowd, M. D., Simon, S. D., & Sharma, V. (2006). Impact of rapid influenza testing at triage on management of febrile infants and young children. Pediatric Emergency Care, 22(3), 145.

Alere. (2017). https://alere.com

Allen, U. D., Aoki, F. Y., Stiver, H. G., & for the Canadian Paediatric Society and the Association of Medical Microbiology and Infectious Disease Canada. (2006). The use of antiviral drugs for influenza: Recommended guidelines for practitioners. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie médicale, 17(5), 273-284. doi:10.1155/2006/165940

Aoki, F. Y., Allen, U. D., Stiver, H. G., & Evans, G. A. (2012). The use of antiviral drugs for influenza: Guidance for practitioners 2012/2013. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie médicale, 23(4), e79-e92. doi:10.1155/2012/879141

Armstrong, G. (2001, January 6). Trends in infectious disease mortality in the United States during the 20th century. (CDC, Ed.). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9892452

Arriola, C., Garg, S., Anderson, E. J., Ryan, P. A., George, A., Zansky, S. M., . . . Chaves, S. S., (2017). influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. Clinical Infectious Diseases, 65(8), 1289-1297. https://doi.org/10.1093/cid/cix468

Bahadoran, A., Lee, S. H., Wang, S. M., Manikam, R., Rajarajeswaran, J., Raju, C. S., & Sekaran, S. D. (2016). Immune responses to influenza virus and its correlation to age and inherited factors. Frontiers in Microbiology, 7 doi:10.3389/fmicb.2016.01841

Barberis, I., Myles, P., Ault, S. K., Bragazzi, N. L., & Martini, M. (2016). History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. *Journal of Preventive Medicine and Hygiene*, *57*(3), E115–E120.

Bell, J., Bonner, A., Cohen, D. M., Birkhahn, R., Yogev, R., Triner, W., . . . Selvarangan, R. (2014). Multicenter clinical evaluation of the novel alere™ i influenza A&B isothermal nucleic acid amplification test. Journal of Clinical Virology : The Official Publication of the Pan American Society for Clinical Virology, 61(1), 81. doi:10.1016/j.jcv.2014.06.001

Bell JJ, Selvarangan R. Evaluation of the Alere i influenza A&B nucleic acid amplification test by use of respiratory specimens collected in viral transport medium. J Clin Microbiol. 2014;52(11):3992e3995.

Belongia, E. A., Simpson, M. D., King, J. P., Sundaram, M. E., Kelly, N. S., Osterholm, M. T., McLean, H. Q. (2016). Variable influenza vaccine effectiveness by subtype: A systematic review and meta-analysis of test-negative design studies. The Lancet Infectious Diseases, 16(8), 942-951. http://dx.doi.org/10.1016/S1473-3099(16)00129-8

Billings, M. (2005). The influenza Pandemic of 1918. Retrieved November 13, 2017, from https://virus.stanford.edu/uda/

Bonner, A. B., Monroe, K. W., Talley, L. I., Klasner, A. E., & Kimberlin, D. W. (2003). Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: Results of a randomized, prospective, controlled trial. Pediatrics, 112(2), 363-367. doi:10.1542/peds.112.2.363

The British Medical Journal. (1918). The Influenzal Pandemic. *The British Medical Journal, 2(3002)*, 39.

Centers for Disease Control and Prevention (CDC). (1999). Achievements in Public Health, 1900-1999: Control of Infectious Diseases. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm

Centers for Disease Control and Prevention (U.S.). (1999). Neuraminidase inhibitors for treatment of influenza A and B infections

Centers for Disease Control and Prevention (CDC). (2016). Clinical Signs and Symptoms of influenza. Retrieved from https://www.cdc.gov/flu/professionals/acip/clinical.htm

Centers for Disease Control and Prevention (CDC). (2015). Cover Your Cough. Retrieved from https://www.cdc.gov/flu/protect/covercough.htm

Centers for Disease Control and Prevention (CDC). (2017). Death and Mortality. Retrieved from https://www.cdc.gov/nchs/fastats/deaths.htm

Centers for Disease Control and Prevention (CDC). (2016). Estimating Seasonal influenza-Associated Deaths in the United States. Retrieved from https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm#how-many-die

Centers for Disease Control and Prevention (CDC). (2017). Flu Vaccination Coverage, United States, 2015-16 Influenza Season. Retrieved from https://www.cdc.gov/flu/fluvaxview/coverage-1516estimates.htm

Centers for Disease Control and Prevention (CDC). (2016). [Flyer on preventative actions against flu October 24, 2016]. Everyday preventive actions that can help fight germs, like flu. Retrieved from https://www.cdc.gov/flu/pdf/freeresources/updated/everyday-preventive-actions-8.5x11.pdf

Centers for Disease Control and Prevention (CDC). (2017). Historical Reference of Seasonal influenza Vaccine Doses Distributed. Retrieved from https://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm

Centers for Disease Control and Prevention (CDC). (2017). How influenza Spreads. Retrieved from https://www.cdc.gov/flu/about/disease/spread.htm

Centers for Disease Control and Prevention (CDC). (2017). Key Facts About influenza (Flu). Retrieved from https://www.cdc.gov/flu/keyfacts.htm

Centers for Disease Control and Prevention (CDC). (2017). Key Facts About Seasonal Flu Vaccine. Retrieved from https://www.cdc.gov/flu/protect/keyfacts.htm

Centers for Disease Control and Prevention (CDC). (2012). Principles of Epidemiology in Public Health Practice, Third Edition: An Introduction to Applied Epidemiology and Biostatistics. Retrieved from https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section9.html

Centers for Disease Control and Prevention (CDC). (2012). Respiratory Hygiene/Cough Etiquette in Healthcare Settings. Retrieved from https://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm

Centers for Disease Control and Prevention (CDC). (1963). Wellbee says: be clean and WASH YOUR HANDS!. Retrieved from https://stacks.cdc.gov/view/cdc/27580

Chapin KC, Flores-Cortez EJ. Performance of the molecular Alere i influ- enza A&B test compared to that of the Xpert flu A/B assay. J Clin Micro- biol. 2015;53(2):706e709.

Connor, S. (2000). Flu epidemic traced to Great War transit camp. Retrieved from https://archive.is/20090808003837/http://www.independent.co.uk/life-style/health-and-wellbeing/health-news/flu-epidemic-traced-to-great-war-transit-camp-728112.html

Cowling, B. J., Ip, D. K. M., Fang, V. J., Suntarattiwong, P., Olsen, S. J., Levy, J., … Simmerman, J. M. (2013). Aerosol transmission is an important mode of influenza A virus spread. Nature Communications, 4, 1935. http://doi.org/10.1038/ncomms2922

Discovery Education. (2000). [Educational documentary]. An Inside Look at the Flu.

Doshi, P. (2008). Trends in Recorded influenza Mortality: United States, 1900–2004. *American Journal of Public Health*, *98*(5), 939–945. http://doi.org/10.2105/AJPH.2007.119933

Dowell, S. F. (2001). Seasonal variation in host susceptibility and cycles of certain infectious diseases. Emerging Infectious Diseases, 7(3), 369-374. 10.3201/eid0703.017301

Dunn J, Obuekwe J, Baun T, et al. Prompt detection of influenza A and B viruses using the BD VeritorTM System Flu AþB, Quidel® Sofia® influenza AþB FIA, and Alere BinaxNOW® influenza A&B compared to real-time reverse transcription-polymerase chain reaction (RT-PCR). Diagn Micro- biol Infect Dis. 2014;79(1):10e13.

Fedson, D. S. (2003). Pandemic influenza and the global vaccine supply. Clinical Infectious Diseases, 36(12), 1552-1561. doi:10.1086/375056

Fisher Scientific. (2018) http://fishersci.com

Fukuyama, S., & Kawaoka, Y. (2011). The pathogenesis of influenza virus infections: The contributions of virus and host factors. Current Opinion in Immunology, 23(4), 481-486. doi:10.1016/j.coi.2011.07.016

Gamblin, S. J., & Skehel, J. J. (2010). influenza hemagglutinin and neuraminidase membrane glycoproteins. The Journal of Biological Chemistry, 285(37), 28403-28409. doi:10.1074/jbc.R110.129809

Garrett, F. (2016). MICR 420 Emerging and Re-Emerging Infectious Diseases. Retrieved January 28, 2018, from http://slideplayer.com/slide/7909622/

Greatorex, J. S., Digard, P., Curran, M. D., Moynihan, R., Wensley, H., Wreghitt, T., . . . Nguyen-Van-Tam, J. S. (2011). Survival of influenza A(H1N1) on materials found in households: Implications for infection control. PloS One, 6(11), e27932. 10.1371/journal.pone.0027932

H5N1 influenza. (2017). Retrieved November 27, 2017, from http://www.who.int/influenza/human_animal_interface/avian_influenza/h5n1_research/faqs/en/

Hassan F, Nguyen A, Formanek A, et al. Comparison of the BD Veritor System for Flu AþB with the Alere BinaxNOW influenza A&B card for detection of influenza A and B viruses in respiratory specimens from pediatric patients. J Clin Microbiol. 2014;52(3):906e910.

Hayden, F., Osterhaus, A., Treanor, J., Fleming, D. M., Aoki, F., Nicholson, K. G., . . . Wightman, K. (1997). Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. New England Journal of Medicine, 337(13), 874-880.

Hazelton B, Gray T, Ho J, et al. Detection of influenza A and B with the AlereTM I influenza A & B: a novel isothermal nucleic acid amplification assay. influenza Other Respir Viruses. 2015;9(3): 151e154.

Hazelton B, Nedeljkovic G, Ratnamohan VM, et al. Evaluation of the Sofia Influenza A þ B fluorescent immunoassay for the rapid diagnosis of influenza A and B. J Med Virol. 2015;87:35e38.

Henderson, D. (2013, December 13). The 1957 pandemic: Not the Flu We Knew. Retrieved from https://www.wnyc.org/story/298086-not-flu-we-knew-jittery-panel-during-1957-58-influenza-epidemic/

HHS Pandemic influenza Plan Update [PDF]. (2017, June). Atlanta: Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD).

Homeland Security Council (U.S.). (2007). National strategy for pandemic influenza implementation plan: One year summary. (). Washington, D.C.: Homeland Security Council.

Hueston, W. J., & Benich, 3., Joseph J. (2004). A cost-benefit analysis of testing for influenza A in high-risk adults. Annals of Family Medicine, 2(1), 33-40. doi:10.1370/afm.34

Hurt, A. C., Alexander, R., Hibbert, J., Deed, N., & Barr, I. G. (2007). Performance of six influenza rapid tests in detecting human influenza in clinical specimens. Journal of Clinical Virology, 39(2), 132-135. doi:10.1016/j.jcv.2007.03.002

Hutchins, S. S., Truman, B. I., Merlin, T. L., & Redd, S. C. (2009). Protecting vulnerable populations from pandemic influenza in the united states: A strategic imperative. American Journal of Public Health, 99(S2), S243-S248. 10.2105/AJPH.2009.164814

Infection Control. (2016). Retrieved November 26, 2017, from https://www.cdc.gov/infectioncontrol/

Institute of Medicine. (2010). The Domestic and International Impacts of the 2009-H1N1 influenza A Pandemic. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK52789/

Jackson, C. (2009). History lessons: the Asian Flu pandemic. Retrieved November 13, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2714797/

Jhung, M. (2011). Epidemiology of 2009 Pandemic influenza A (H1N1) in the United States. Retrieved from https://academic.oup.com/cid/article/52/suppl_1/S13/498323

Jokela P, Vuorinen T, Waris M, Manninen R. Performance of the Alere i influenza A&B assay and mariPOC test for the rapid detection of influenza A and B viruses. J Clin Virol. 2015;70:72e76.

The Journal of the American Medical Association (1918). *The Influenza Outbreak. The Journal of the American Medical Association, 71*, 1138.

Kawaoka, Y. (2004). preface. International Congress Series, 1263, v. doi:10.1016/j.ics.2004.04.029

Kentaro, S. (1997). History of influenza epidemics and discovery of influenza virus. *US National Library of Medicine*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9360364

Kilbourne, E. D. (2006, January). influenza Pandemics of the 20th Century. Retrieved November 13, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291411/

Klenk, H. D., & Garten, W. (1994). Host cell proteases controlling virus pathogenicity. Trends in Microbiology, 2(2), 39.

Lanzavecchia, A. (1985). [Nature. 1985 Apr 11-17;314(6011):537-9.] Antigen-specific interaction between T and B cells. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/3157869

Lee CK, Cho CH, Woo MK, et al. Evaluation of Sofia fluorescent immunoassay analyzer for influenza A/B virus. J Clin Virol. 2012;55: 239e243.

Leonardi GP, Wilson AM, Zuretti AR. Comparison of conventional lateral- flow assays and a new fluorescent immunoassay to detect influenza vi- ruses. J Virol Methods. 2013;189(2):379e382.

Lewandrowski K, Tamerius J, Menegus M, et al. Detection of influenza A and B viruses with the Sofia analyzer: a novel, rapid immunofluorescence-based in vitro diagnostic device. Am J Clin Pathol. 2013;139(5):684e689.

Lim, Andrew. Natural Alternatives to Tami-Flu Medication. Retrieved February 9, 2017. Retrieved from http://www.odec.ca/projects/2012/limlia/Index.html

Lofgren, E., Fefferman, N. H., Naumov, Y. N., Gorski, J., & Naumova, E. N. (2007). Influenza seasonality: Underlying causes and modeling theories. Journal of Virology, 81(11), 5429-5436. 10.1128/JVI.01680-06

Lowen AC, Mubareka S, Steel J, Palese P. (2007). Influenza Virus Transmission Is Dependent on Relative Humidity and Temperature. PLoS Pathog 3(10): e151. https://doi.org/10.1371/journal.ppat.0030151

McLean, H. Q., Belongia, E. A., Kieke, B. A., Meece, J. K., & Fry, A. M. (2015). Impact of late oseltamivir treatment on influenza symptoms in the outpatient setting: Results of a randomized trial. Open Forum Infectious Diseases, 2(3), ofv100.

Monto, M. A. (2000). Clinical Signs and Symptoms Predicting influenza Infection. Retrieved November 20, 2017, from https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/485554

MPH, M. B. (2005). Management of influenza Symptoms in Healthy Children. Retrieved November 20, 2017, from https://jamanetwork.com/journals/jamapediatrics/fullarticle/486172

National response framework released. (2008). Fire Chief (Online Exclusive),

Nam MH, Jang JW, Lee JH, et al. Clinical performance evaluation of the BD Veritor System Flu AþB assay. J Virol Methods. 2014;204: 86e90.

S, Roth RB, Stiles J, et al. Evaluation of Alere i influenza A&B for rapid detection of influenza viruses A and B. J Clin Microbiol. 2014;52(9): 3339e3344.

Noh JY, Choi WS, Lee J, et al. Clinical performance of the Sofia TM influenza AþB FIA in adult patients with influenza-like illness. Diagn Microbiol Infect Dis. 2015;83:130e132.

Noyce, J. O., Michels, H., & Keevil, C. W. (2006). Potential use of copper surfaces to reduce survival of epidemic meticillin-resistant staphylococcus aureus in the healthcare environment. Journal of Hospital Infection, 63(3), 289-297. 10.1016/j.jhin.2005.12.008

Occupational Safety and Health Administration (OSHA). (2017). Retrieved January 18, 2018, from https://www.osha.gov/Publications/OSHA3079/osha3079.html

Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services. (2007). Office of the assistant secretary for preparedness and response; HHS public health emergency medical countermeasures enterprise implementation plan for chemical, biological, radiological and nuclear threats. notice. Federal Register, 72(77), 20117.

Otter, J. (2016). Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. Retrieved January 28, 2018, from https://www.sciencedirect.com/science/article/pii/S0195670115003679

Pawaiya, R. (2009). Swine flu and the current influenza A (H1N1) pandemic in humans: A review. Retrieved January 28, 2018, from https://www.researchgate.net/publication/229805901_Swine_flu_and_the_current_influenza_A_H1N1_pandemic_in_humans_A_review

Professional Disposables International. (2018). *Environment of Care Super Sani-Cloth Germicidal Disposable Wipes*. https://pdihc.com/all-products/super-sani-cloth

Pelsue, Stephen. (2016). Fundamentals of Immunoassays. Retrieved January 21, 2018, from http://mainebiotechnology.com/fundamentals-of-immunoassays/

Perry, K. A., Coulliette, A. D., Rose, L. J., Shams, A. M., Edwards, J. R., & Noble-Wang, J. A. (2016). Persistence of influenza A (H1N1) virus on stainless steel surfaces. Applied and Environmental Microbiology, 82(11), 3239-3245. 10.1128/AEM.04046-15

Pike, J. (2011). 1968 Hong Kong Flu. Retrieved November 13, 2017, from https://www.globalsecurity.org/security/ops/hsc-scen-3_pandemic-1968.htm

Poehling, K. A., Zhu, Y., Tang, Y., & Edwards, K. (2006). Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. Archives of Pediatrics & Adolescent Medicine, 160(7), 713-718. doi:10.1001/archpedi.160.7.713

Potter, C. W. (2001). A history of influenza. *Journal of Applied Microbiology,91*(4), 57-579. Retrieved November 20, 2017, from http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2672.2001.01492.x/full?wol1URL=/doi/10.1046/j.1365-2672.2001.01492.x/full®ionCode=US-NY&identityKey=2f6b0318-a328-4772-abb9-60ff213e13ef

Powers, J. (2016, January 5). Development of the Flu-PRO: a patient-reported outcome (PRO) instrument to evaluate symptoms of influenza. Retrieved January 28, 2018, from https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-015-1330-0

Quidel. (2018). http://quidel.com

Rifkind, J. M., Shin, Y. A., Heim, J. M., & Eichhorn, G. L. (1976). Cooperative disordering of single-stranded polynucleotides through copper crosslinking. Biopolymers, 15(10), 1879.

Rothberg, M. B., He, S., & Rose, D. N. (2003). Management of influenza Symptoms in Healthy Adults. Retrieved November 20, 2017, from http://onlinelibrary.wiley.com/doi/10.1046/j.1525-1497.2003.20822.x/full

Rozo, M., & Gronvall, G. K. (2015). The Reemergent 1977 H1N1 Strain and the Gain-of-Function Debate. Retrieved November 13, 2017, from http://mbio.asm.org/content/6/4/e01013-15.full

Sealey, A. (2010). Influenza Pandemics Now, Then, and Again. Current Events in Historical Perspective, 3(8). Retrieved February 4, 2018, from http://origins.osu.edu/article/influenza-pandemics-now-then-and-again

Shaman, J., Kohn, M., & Singer, B. H. (2009). Absolute humidity modulates influenza survival, transmission, and seasonality. Proceedings of the National Academy of Sciences of the United States of America, 106(9), 3243-3248. 10.1073/pnas.0806852106

Shi, L., & Stevens, G. D. (2005). Vulnerability and unmet health care needs: The influence of multiple risk factors. Journal of General Internal Medicine, 20(2), 148-154. 10.1111/j.1525-1497.2005.40136.x

Siegel JD., Rhinehart E., Jackson M., Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. (2007). Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings

Taubenberger, J. K., & Morens, D. M. (2006). 1918 influenza: the Mother of All Pandemics. Retrieved November 13, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291398/

Taubenberger, J. K., & Morens, D. M. (2007). The pathology of influenza virus infections. Annual Review of Pathology: Mechanisms of Disease, , 71015171337001. doi:10.1146/annurev.pathol.3.121806.154316

Tellier, R. (2006). Review of Aerosol Transmission of influenza A Virus - Volume 12, Number 11—November 2006 - Emerging Infectious Disease journal - CDC. https://doi.org/10.3201/eid1211.060426

Thomas, Y., Boquete-Suter, P., Koch, D., Pittet, D., Kaiser, L., & Zupanc, T. A. (2014). Survival of influenza virus on human fingers. Clinical Microbiology and Infection, 20(1), O58-O64. 10.1111/1469-0691.12324

Thompson, W. W., Shay, D. K., Weintraub, E., Brammer, L., Cox, N., Anderson, L. J., & Fukuda, K. (2003). Mortality associated with influenza and respiratory syncytial virus in the united states. Jama, 289(2), 179-186. doi:10.1001/jama.289.2.179

Trabattoni, E., Le, V., Pilmis, B., Pean de Ponfilly, G., Caisso, C., Couzigou, C., . . . Nguyen Van, J. (2017). Implementation of Alere i influenza A & B point of care test for the diagnosis of influenza in an emergency department. The Journal of Emergency Medicine. doi: http://dx.doi.org/10.1016/j.ajem.2017.10.046

Treanor, J. J., Talbot, H. K., Ohmit, S. E., Coleman, L. A., Thompson, M. G., Cheng, P., . . . Shay, D. K. (2012).Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clinical Infectious Diseases, 55(7), 951-959. https://doi.org/10.1093/cid/cis574

Viboud, C. (2005). Multinational Impact of the 1968 Hong Kong influenza Pandemic: Evidence for a Smoldering Pandemic. Retrieved from https://academic.oup.com/jid/article/192/2/233/856805

Viboud, C. (2016). Global Mortality Impact of the 1957–1959 influenza Pandemic. Retrieved from https://academic.oup.com/jid/article/213/5/738/2459470/Global-Mortality-Impact-of-the-1957-1959-influenza

Weinstein, R. A., Bridges, C. B., Kuehnert, M. J., & Hall, C. B. (2003). Transmission of influenza: Implications for Control in Health Care Settings. Clinical Infectious Diseases, 37(8), 1094–1101. https://doi.org/10.1086/378292

Worcester Polytechnic Institute (WPI) Residential Services. (2017). *The Flu & What to Do* [Poster]. Worcester Massachusetts.

Zimmerman, R. K., Nowalk, M. P., Chung, J., Jackson, M. L., Jackson, L. A., Petrie, J. G., . . . Fry, A. M. (2016). 2014-2015 influenza vaccine effectiveness in the United States by vaccine type. Clinical Infectious Diseases, 63(12), 1564-1573. https://doi.org/10.1093/cid/ciw635