Bryant University

HONORS THESIS

# An In-Depth Look at Recent Influenza Seasons and Vaccine Effectiveness

BY: Ariana Ricci

ADVISORS • Kirsten Hokeness & Stephanie Mott

---

Submitted in partial fulfillment of the requirements for graduation
with honors in the Bryant University Honors Program

APRIL 2013

## Table of Contents

## ABSTRACT

This paper aims to present an in-depth exploration of immunology, the influenza virus, vaccination, and vaccination's effectiveness with respect to influenza. It also delves into the possible causes behind the large increase in early childhood deaths during the 2003-2004 influenza season, which was a turning point in terms of influenza incident reporting. Finally, data analysis on the relationship between childhood flu vaccine coverage and childhood outpatient ILI (influenza-like illness) visits by region is presented as a measurement of vaccine effectiveness and identifier of trends. Although this relationship was not statistically significant (alpha=0.05) regionally, this simply points to alternate factors that exist among the relationship between vaccine coverage and outpatient visits in children. The same comparison made over time with national statistics did prove statistically significant (p=0.02), however, other variables are hypothesized to be present in this relationship as well.

# INTRODUCTION & LITERATURE REVIEW

There are many wonders of modern medicine that we now take for granted in the 21st century. As such, we accept these practices as commonplace. One of these marvels is vaccination. Though this practice is over two centuries old, most vaccines have only been around since the mid-1900s, with many being widely recommended just in the last few decades. Since then, many controversies have arisen over vaccine safety, effectiveness, and ethics. The focus, though, should remain on the science behind the vaccines and what makes some more effective at eradicating disease than others, as well as how immunization is affecting children.

The idea for this paper began when a study of influenza and vaccines led to the discovery of an unusually large number of childhood flu deaths during the 2003-2004 flu season, which was a turning point in terms of influenza incident reporting. This spurred the idea of conducting an original study on influenza vaccine effectiveness in children based on rates of vaccine coverage vs. outpatient rates due to flu by region. Although the study of influenza and vaccines is ever-growing and the body of knowledge increasing daily, this study may shed some light on fundamental relationships between the flu and its vaccine that are not always presented in an objective manner by the media.

## Immune System Components & Processes

In order to fully delve into the science of vaccination, it is first necessary to understand their effect on the immune system. Generally, immunity is separated based on whether it is innate or adaptive. Within each of these arms of the immune system are both cellular (direct cell contact) and humoral (non-direct cell contact) components. Innate immunity is present from birth and confers protection from pathogens regardless of whether or not the body has been exposed to them before. In this way, it is regarded as the first line of defense. One component of the innate immune system includes physical, anatomical barriers such as the skin and inner epithelial layers. Other components are the phagocytic leukocytes, which are white blood cells that engulf and digest microorganisms, as well as dendritic cells, which present antigens on the surface of cells. Next is a special type of lymphocyte (a white blood cell) known as a natural killer (NK) cell. These cells are capable of destroying any and all infected cells, as well as tumor cells. Finally, the last aspect of the innate immune system is the presence of circulating plasma proteins, which are known as the complement system. These proteins

become activated in the presence of a pathogen, to which they bind. By interacting with macrophage receptors, complement proteins trigger phagocytosis (Janeway & Travers, 1996).

In contrast, adaptive immunity is known as the body's second line of defense against pathogens. It is only called into action if and when the innate immune system fails to thwart an invading agent, and accordingly requires more time to respond to an attack. However, they do retain immunological memory of the pathogens they fight, thus minimizing the time needed to react to future incidents. The reason behind this is the antigen-specific nature of innate immunity, meaning that this system is only able to recognize and respond to antigens it has previously been exposed to, so memory of these antigens is crucial to its success. The adaptive immune system's humoral defense includes B lymphocytes or B cells, which are produced in the bone marrow. These cells create antibodies, plasma proteins also known as immunoglobulins. They either bind specifically to molecules from the invading pathogen in order to neutralize it or recruit other cells to destroy the pathogen by way of phagocytosis. Secondly, the cell-mediated immune response of the adaptive immune system is based on T lymphocytes or T cells, of which there are two kinds. The first is CD8+ cytotoxic T cells, which directly kill cells infected with viruses, while the second type, CD4+ helper T cells, activate B cells and macrophages to then rid the body of these pathogens (Janeway & Travers, 1996).

Influenza

Technically speaking, influenza or "the flu" is an acute viral, respiratory illness caused by one of many flu viruses discovered in the early 1930s. This general definition, however, does not begin to underscore the severity and impact of this illness. Typically, the flu affects the nose, throat, lungs, and airways. It is different from the common cold in that it causes a 2-3 day fever, headaches, a lingering cough, and extreme fatigue and muscle and joint aches. Upper respiratory ailments such as stuffy nose, sneezing, and sore throat may occur, but are not always present with the flu (Chang, 2011). Although many patients will recover after about one week, many may still feel the effects of the flu weeks later in the form of a cough or low energy levels (Flu Overview, 2012).

Influenza is a seasonal epidemic that happens each year mainly during the late fall and winter months in most temperate regions and can last until early spring. For the northern hemisphere, the flu season runs from October to March. In tropical climates, the flu can circulate year-round and peak once or twice during rainy seasons. Influenza spreads easily, especially in confined, crowded spaces like schools, nursing homes, and the workplace. Transmission occurs when a sick person expels infected droplets into the air by sneezing or coughing. A person in the area may then breathe them in and become sick. In addition, influenza can spread by touching contaminated surfaces and then putting one's hands near the face (mouth, nose, eyes). This is why covering the mouth and nose when sneezing or coughing is so important, as is frequent hand-washing (Influenza, 2009).

There are three types of influenza: A, B, and C. Types A and B are typically associated with seasonal epidemics, while type C is quite mild and does not generate cause for concern. Type A is the most common type and produces the most acute symptoms, while type B is similar to A with less serious symptoms. It is also slightly less common. Influenza A is further broken down into subtypes categorized by the two surface proteins on the virus. These antigens are the portions of the virus that evoke an immune response. The first protein is hemagglutinin (H), of which there are 17 different subtypes, while the second is neuraminidase (N), of which there are 10 subtypes. Together, these form the complete subtype name, such as H5N1 or H7N2. Within each subtype, there can be several different strains that develop in a season, and are simply numbered (Types, 2012).

What makes the influenza virus so difficult to treat and prevent is its uncanny ability to change very often and so easily. One type of change is an antigenic drift. This is when new variants of a strain form each year due to genetic mistakes during the virus's replication. The new variant prevails due to pressure from the immune system's antibodies that are fighting the original strain. This process could cause one to catch the flu twice in the same season due to the slight shift in the antigen and subsequent lack of antibodies to fight it. It is important to note that both influenza A and B are subject to antigenic drifting (Antigenic Drift, 2011). The second way in which flu changes is the more noticeable antigenic shift. This phenomenon, on the other hand, has only been observed in type A. This is an abrupt, major change that results in a new virus subtype, rather than just a new strain. A shift happens when two different

strains simultaneously infect a cell. Antigens (hemagglutinin and/or neuraminidase) are exchanged and genetic material is reassorted to form the new virus subtype. Additionally, antigenic shift is the process that allows a strain to transfer from one animal species to another or from human to animal and vice versa (Antigenic Shift, 2011).

Each year, approximately five to twenty percent of Americans become infected with influenza. This results in over 200,000 hospitalizations and anywhere from 3,000 to 49,000 deaths in the U.S. annually. The reason for this wide range, which was compiled from the last thirty years, is the unpredictability of the flu's severity in any given season. Also, there are logistical issues that contribute to this lack of accuracy in number of deaths. The first is that there is a lack of reporting by each state since they are not mandated to report seasonal flu deaths of those individuals over 18. Another problem is that influenza is not necessarily cited on death certificates, since fatalities often occur from complications of the flu, rather than simply the flu itself. One other explanation is that these flu-related deaths happen a few weeks post initial infection either due to a bacterial co-infection like pneumonia or exacerbation of an existing illness, such as heart disease or chronic obstructive pulmonary disease (COPD). In this case, the patient may not be tested for influenza, or the flu would not be detected in a test at this later point in time (Estimating, 2011).

Often, 36,000 is quoted as an average number of U.S. influenza deaths per year, though the aforementioned range (3,000-49,000) is a more accurate representation of the virus's irregularity. This average was gleaned from a study conducted by the Centers for Diseases Control and Prevention (CDC) in 2003. Because of the issues mentioned previously, the CDC developed a model using respiratory and circulatory (R&C) deaths as a base for influenza death estimates. Specifically, it was done using Poisson regression models with national viral surveillance data for the 1976-1999 flu seasons. The reason why the CDC uses R&C deaths as opposed to pneumonia and influenza (P&I) deaths as the baseline for estimating influenza deaths is because R&C deaths includes any fatalities due to cardiac or respiratory complications that are caused by influenza. Therefore, it is more sensitive to influenza fatalities as a whole (Estimating, 2011).

Despite the fact that the flu can majorly affect those of any age, young children (under 2) the elderly (over 65), pregnant women, and those with chronic medical conditions have the highest risk for complications. This is due to their lack of protection stemming from either immature or compromised immune systems. Specifically, those with conditions such as asthma, neurological disorders, chronic lung diseases, heart disease, disorders of the blood, endocrine, kidney, liver or metabolism, HIV/AIDS, cancer, or morbid obesity are at high risk for flu-related issues (People, 2012).

History & Classification of Flu

It seems that influenza or "the flu" may in fact be almost as old as the father of medicine himself, Hippocrates. He described an illness similar to the flu in Greece in 412 B.C. This "sweating sickness" passed through Britain with a vengeance, causing many fatalities mainly due to the lack of effective treatments at the time. It was not until 1918 that the first influenza pandemic occurred, commonly referred to as the Spanish flu. The actual type and subtype of flu was later classified as A (H1N1). Over 100 million deaths have been attributed to this pandemic, which overwhelmed the healthcare system and caused the life expectancy in the U.S. to drop by twelve years. Oddly, it seemed to affect those who were young and healthy by causing the immune system to become overworked. Despite the public health habits put into place, such as requiring citizens to wear masks in public, the virus ravaged the world that year, stopping only after it had "burned itself out" (Walsh, 2009).

More recent pandemics have fortunately been milder, but there is always a looming fear of another 1918 bout of the flu. The pandemics in 1957 (Asian flu, A/H2N2) and 1968 (Hong Kong flu, A/H3N2) were tame in comparison to the Spanish flu, but still carried heavy death tolls of about 2 million and 1 million, respectively. Most recently came the swine flu pandemic of 2009, which was responsible for just over 18,000 deaths worldwide (Pandemic, 2010) (See Figure 1). Although it was the same subtype of virus as the Spanish flu and sickened most seriously the same group of people, the impact was not as severe. Perhaps this is due to the great strides in healthcare that have been made since this time in both hygiene, a stronger encouragement of preventative measures such as hand-washing, antiviral medications to curb the flu's symptoms, respirators, and of course, vaccines. In general, strain A (H3N2) has caused more than double the number of deaths as other A or B strains have

throughout history. This reveals the virulence or disease-producing power of this virus subtype. One study attributed this to the fact that even small strain differences in H3N2 viruses can mitigate the protective ability of prior antibodies to the virus. In this way, recurring epidemics can take place in those of all ages, being especially fatal in the elderly (Wright, Thompson, & Karzon, 1980).

| Date | Strain | Subtype | Common Names |
|---|---|---|---|
| 1918 | A | H1N1 | "Spanish" flu |
| 1957 | A/Singapore/57 | H2N2 | "Asian" flu |
| 1962 | A/Japan/62 | H2N2 | Epidemic |
| 1964 | A/Taiwan/64 | H2N2 | Epidemic |
| 1968 | A/Aichi/68 | H3N2 | "Hong Kong" flu |
| 1976 | A/New Jersey/76 | H1N1 | Swine flu in recruits |
| 1977 | A/USSR/77 | H1N1 | "Russian" flu |
| 2009 | A/California/09 | H1N1 | “Swine flu” A(H1N1) |

*Figure 1 – Influenza Pandemics & Their Classifications*

In an article by Morens, Folkers, and Fauci (2009), a pandemic is identified not only by its wide geographic expanse and movement, but also by its high infection rate and the speed with which it spreads. Also, the population typically has little to no immunity to the disease due to the novelty of it, which makes it much more infectious, contagious, and severe in nature. An epidemic is similar to a pandemic, except that it is not necessarily global or quite as widespread in its extension. It is declared when the number of new cases in a population over a certain time exceeds the expected incidence rate. Finally, an outbreak is an epidemic that is limited to a small region or community (Folkers, Morens, & Fauci, 2009).

Vaccination

Inoculation, the process of introducing immunologically active material into an organism to prevent or treat disease, is believed to have begun in India or China prior to 200 B.C.

However, not much was known or recorded about it until much more recently. British physician Edward Jenner is consistently hailed as the "father of modern vaccinology," and with good reason. In 1796, he developed the more specific procedure known as vaccination, or the "inoculation of healthy individuals with weakened or attenuated strains of disease-causing agents to provide protection from disease" (Janeway & Travers, 1996, p. 1-1). The purpose of this is to induce an immune response and the subsequent production of antibodies so that the body will be able to fight off the actual virus or bacterium upon exposure to it. Jenner created a vaccine to prevent smallpox by infecting a young boy with cowpox, which was similar in nature to smallpox, yet much less dangerous. Since hypodermic syringes had not yet been developed, Jenner simply used a lancet to scratch some of the infectious substance into the boy's arm. Sure enough, the boy became sick with cowpox. Almost two months later, Jenner inserted the smallpox virus into him and witnessed no sickness—a success. Thus, this form of inoculation was named a vaccine, after the Latin word "vacca," meaning cow (Merino, 2010, p.13).

By mimicking a natural infection, vaccines train the immune system to fight off the pathogen should it enter the body. First, the innate immune system is activated. Macrophages in the body recognize the antigen proteins that are contained in the vaccine solution just as if it was due to an actual virus. This signals the adaptive immune system to gear up, first with a surge of T cells binding to the infected cells. Then, B cells secrete antibodies that also help to bind to the antigens and neutralize the pathogen. Once the infection is overcome by the immune system, memory B and T cells are created so that the body can respond even quicker and more efficiently next time (Understanding Vaccines, 2008).

Vaccine popularity soared in the middle of the nineteenth century with the advent of hypodermic syringes. It was during this time that vaccines for cholera, rabies, tetanus, typhoid fever, and bubonic plague were created. The twentieth century saw the addition of polio, measles, mumps, and rubella vaccines. Today, they are still widely attributed to the disappearance of smallpox and polio in the U.S., though not without opposition. Vaccines have been at the center of controversy in recent years due to their purported connection to autism in children (though this has been largely accepted as false in the medical community

following studies), unsafe side effects, and possible violation of religious and personal freedoms (Merino, 2010).

Generally, however, vaccines are indeed viewed as a medical blessing. Not only do they act as a preventative measure in individuals, but they also aid in community-acquired or herd immunity. This occurs when an adequate amount of people in the population are vaccinated against a disease, thus lowering the entire group's likelihood of falling ill. The challenge has always been reaching this critical number of people, though. Evidence of the consequences of low immunization rates have been shown in recent years. For example, in 1974, Japan declared it unnecessary to vaccinate against pertussis due to its declined prevalence. In just five years, pertussis had been able to infect 13,000 and kill 41, revealing the necessity of the vaccine even in modern times. Additionally, a measles outbreak occurred in the U.S. in 1989 at a time when vaccination rates against the disease were very low. Sadly, 55,000 cases of measles were recorded that year, as well as 136 deaths. This too supports the notion that continued vaccination efforts are fundamental to keeping infection rates low (Understanding Vaccines, 2008).

Overview of the Influenza Vaccine

Specifically, a vaccine for influenza was developed in the 1950s, during a time when immunization was becoming increasingly popular. Prior to this in 1936, two influenza A vaccines were developed in embryonic eggs. One was a live virus created by Wilson Smith, while the other was a killed, whole virus prepared by Thomas Francis and Thomas Magill. Although Smith's vaccine was later determined to have an unacceptable fail rate (20% of vaccinated patients contracted febrile influenza), it paved the way for live virus vaccination. Throughout the 1940s, Francis and Magill experimented with different types of live virus vaccines and ran into problems regarding mutation and inconsistent attenuation upon replication. It was not until 1968 that influenza vaccines were licensed for use in the U.S. Not until 2004 were they added to the pediatric immunization schedule (Plotkin & Plotkin, 2008).

Today, influenza vaccines are still produced in the same manner, though in mass numbers and in a safer fashion. That is, chick embryos are inoculated with the chosen influenza viruses. Then, the mixture is left to cultivate for many weeks. Next, the flu strain is rendered inactive

by the addition of formaldehyde. Multi-dose vials also contain thimerosal, a mercury derivative, to prevent the possibility of contamination. (Though this substance has not been shown to cause harm, it is only used when needed as a precaution, and has not been added to new vaccines licensed for use in children since 2001.) (Thimerosal, 2012). The final step is when the three virus strains that have been added to the vaccine that year are blended into one vaccine through replication. Also, adjuvants, or ingredients used to improve the immune response, are added to the vaccine. Today, the only FDA-approved adjuvant is alum, which helps to slow the release of antigens and deliver them to the lymph nodes where the immune response is initiated (Understanding Vaccines, 2008).

Prediction and Selection of Influenza Vaccine Strains

Perhaps the most difficult part of the aformentioned process is the decision on which three strains of influenza should be included in the vaccine that season. It is standard for the vaccine to contain one influenza A (H3N2) virus, which is seasonal, one influenza A (H1N1) virus, and one influenza B virus. Scientists must choose the specific strains within these subtypes (e.g., A/California/2004) to be included each year. These predictions are made based on large amounts of surveillance data on past flu seasons, worldwide flu activity, weather patterns, laborartory and clinical studies, and availability of virus strains that are suitable for production. This information is gleaned from 130 national influenza centers in 101 countries. The World Health Organization (WHO) holds two meetings per year (one in February for the Northern Hemisphere and one in September for the Southern Hemisphere) with the directors of their Collaborating Centers for Reference and Research on Influenza, as well as other laboratory directors. WHO then makes official recommendations on the strain choices for the flu vaccines, but ultimately each country has the final say on what to include in their vaccines. In the US, the FDA makes this decision (Selecting, 2011).

New techniques for more advanced and accurate predictions and subsequent selection of influenza virus strains are beginning to surface. One such strategy was developed in 2010 by scientists at Rice University, led by co-authors Michael Deem and Jiankui He. Once a new strain appears, their method can predict whether or not the strain will become dominant, and thus should be included in the vaccine. Often, dominance is difficult to predict in a strain, considering it can take up to three years for it to emerge as such. Pulling information from

GenBank, which is where public health officials post genetic sequences of new flu strains, the scientists utilized multidimensional scaling to create graphical plots of complex data. This allows them to pare down a 329-amino-acid region of the flu virus to just two dimensions that contain the most useful information. Then, all of the points are plotted as a function of these two variables, which is much simpler to work with and highlights clusters of future dominant strains (Multidimensional, 2010).

Current Types of Influenza Vaccines and Recommendations

Currently, there are two main types of influenza vaccine. The most popular is the trivalent inactivated virus (TIV), which contains microbes that have been rendered inert with chemicals, heat, or radiation. In this form, the virus cannot cause disease or mutate back to such a form. Only the antigens, membrane, and genetic material remain present, which are all that is needed to produce a response and thus gain immunity. Another notable benefit of this type of vaccine is that it does not require refrigeration since it can be transported in a freeze-dried state, thus enabling increased access for developing countries. A drawback, however, is that these vaccines generally do not produce as strong of an immune response as live vaccines (Understanding Vaccines, 2008).

The second type of flu vaccine is the live attenuated influenza vaccine (LAIV), which contains a live form of the virus in a weakened or attenuated form. Again, it is not capable of causing the actual disease it is protecting the body against in this state. Being live means that the virus is that much similar to the organism the body will actually be exposed to come flu season. Therefore, it stimulates a stronger immune response, both on a cellular and humoral level. Lifelong immunity may be achieved from significantly fewer doses as compared to inactivated virus vaccines. Unfortunately, the LAIV has its downfalls, such as the possibility of the virus mutating back to its fully virulent form. Unlike the TIV, it must be refrigerated and is therefore not as easily accessible in other countries. Also, this vaccine is not appropriate for those with compromised immune systems (such as the sick, infants, and the elderly). In fact, it is only approved for use in healthy people 2 through 49 years of age who are not pregnant (Key Facts, 2013).

Once the vaccine has been manufactured, the FDA requires rigorous research and testing before permitting the vaccine to be licensed. The first stage is lab and animal testing, also called preclinical testing. Only if it meets expectations and appears safe will it be considered for clinicsl tesing in humans. Before this can occur,an Investigational New Drug (IND) application must be submitted to and approved by the FDA. Only at this point can it be tested in human volunteers. The clinical trials start on a small scale; their increase is contingent upon the success of the vaccine. Once three phases of the clinical trial occur, testing the safety, dosage, and efficacy of the vaccine, an application for license can be submitted to the FDA (Understanding Vaccines, 2008). Of course, researchers cannot deliberately expose volunteers to pathogens to test efficacy, nor are they required to have a control group for testing. In other words, it is deemed unethical to only vaccinate half the study volunteers and not offer them the best possible protection from the flu. Therefore, all of the volunteers are vaccinated and then monitored throughout the flu season to gauge how well the vaccine prevented them from falling ill (Miller, 2002). The last step is to distribute the virus's information to manufacturers and begin production and distribution. For many years, only a few manufacturers were producers of the flu vaccine, essentially monopolizing the market on vaccine production. However, there were six different manufacturers of TIV this past flu season (2012-2013), as well as one manufacturer each for the TIV high dose, TIV intradermal, and LAIV (Seasonal, 2013) (see Appendix A).

The current recommendation given by the Advisory Committee on Immunization Practices (ACIP), a subdivision of the CDC, is that everyone aged 6 months and over should receive an influenza vaccine. One dose is adequate for most people, though it is recommended that children under 9 years old who are receiving influenza vaccine for the first time or who received only 1 dose the previous season (if it was their first vaccination season) should receive 2 doses this season (Kroger, Sumaya, Pickering & Atkinson, 2011). Also, there is a high-dose vaccine, Fluzone, approved for use in those 65 and older. It contains 4 times the amount of antigen in order to invoke a stronger immune response. However, the ACIP and CDC have not expressed an opinion on which dosage is best for the elderly (Fluzone, 2012).

In 2012, the first meta-analysis assessing efficacy and effectiveness of influenza vaccines using sensitive and specific diagnostic tests for influenza was performed. Medline wa sused to

find randomized, controlled trials that assessed reduction in influenza risk after receiving a vaccination. Articles found to be eligible were published between January 1, 1967 and February 15, 2011. In total, 31 studies over 12 seasons were deemed appropriate for use in the meta-analysis. TIV was shown to be efficacious in 67% of the 12 flu seasons analyzed in adults aged 18 to 65 years. In children aged 6 months to 17 years, LAIV showed efficacy in 75% of the seasons. There were no eligible studies for children aged 8 to 17 years, so vaccine effectiveness in this group could not be determined. It was concluded that, overall, influenza vaccines provide moderate protection in many seasons, but very little in other seasons. Protection is even more scarce in the elderly, while young children are the ones who benefit most from LAIVs (Osterholm, Kelley, Sommer, & Belongia, 2012).

Alternative Influenza Vaccine Technology

Unfortunately, the current vaccine production process takes over six months to complete and seems antiquated compared to the great strides that have been reached regarding biomedical technology. Aside from this factor, an extremely large supply of fertile chickens and eggs is needed. The whole process is centered upon how well the virus grows in the eggs, as well as the time that this takes. Therefore, it is nearly impossible to quicken production should a pandemic occur.

On the other hand, growing the virus in living cells rather than eggs (known as cell culture-based production) is both faster and more precise. Production can also be expanded in the case of a pandemic. Another advantage of this method is that it is safe for those with allergies to eggs. Although cell culture-based vaccines are available for most other viruses, such as measles, mumps, and polio, the same cannot be said of the flu virus. Scientists have encountered problems achieving good quality virus yields using the cell culture method, though there is one flu vaccine of this kind licensed for use in Europe. Currently, much time and effort is being put into producing this type of flu vaccine here in the U.S. (Optimizing, 2011).

One promising type of technology is found in DNA-based vaccines, which are advantageous in that they do not require the whole influenza virus to be replicated. Instead, they contain a portion of the flu virus' genetic material that is placed inside a plasmid, or circular strand of

DNA. Once the vaccine is administered, the genetic material is expressed inside a human cell. This leads to the synthesis of flu virus proteins inside the cell, which signals the immune system to respond just as an antigen would. This type of vaccine is currently in several stages of development for diseases such as the flu (New, 2011).

A second type of new technology is the subunit vaccine, which is similar to the DNA-based vaccine since it usually only includes the immune-stimulating antigens of a virus rather than the virus molecules in their entirety (Janeway & Travers, 1996). Identifying which antigens will be most effective is the challenge of this method, but once this has been accomplished, the antigens can be produced using recombinant DNA technology in the lab. In this way, recombinant subunit vaccines differ from DNA-based vaccine since the antigen is made in the lab and then injected, rather than being produced by the host cells. The process begins with the hemagglutinin gene of the influenza virus, which is responsible for binding the virus to the cell it is infecting. This genetic material is then placed into a vector, which is a virus that can only infect other species, such as insects, but is harmless to humans. The vector is then used to deliver the genetic material to a cell culture in the lab. These cells are instructed by the genetic material to produce the antigens, which are then purified and inserted into the vaccine (New, 2011). The first successful vaccine of this kind was for the hepatitis B virus (Janeway & Travers, 1996).

Vectors can also be utilized in a different form. Rather than using the vector as an intermediary step, the entire vector and influenza genetic material may be injected into a patient. Since the vector is a harmless microbe, this method is completely safe, though it may seem unnerving to some. Once inside the body, this vector virus will express the hemagglutinin proteins needed to induce an immune response (New, 2011).

Perhaps the most promising vaccine of its kind is the universal flu vaccine, which would ideally protect against all influenza strains for an extended period of time, such as over decades. The key behind this type of vaccine would be the use of proteins that are present in all types of flu, rather than proteins that are specific to a certain subtype and strain. Some of these include portions of the hemagglutinin protein, viral envelope proteins like M2, and the NP protein, used for viral replication. The hope is that the antibodies produced by the body

upon exposure to these antigens would then recognize subsequent strains and be able to stave off infection. The NIAID was successful in creating and testing a universal flu vaccine in 2010, which did indeed produce antibodies in mice, ferrets, and monkeys based on the hemagglutinin stem (New, 2011). Dr. Gary J. Nabel, head researcher on this study, noted that the stem appears nearly identical in all strains, making it a great target for this vaccine. In fact, the mice and ferrets in the trials produced antibodies to flu strains dating as far back as 1934 and as recent as 2006 and 2007. As of 2010, Dr. Nabel estimated human trials being three to five years away (NIH, 2010).

More recently, a biopharmacetuical company based in Madison, WI called FluGen has been developing their own version of a universal flu vaccine, REDEE FLU. It is desgined to not only protect against known strains, but also strains that have yet to circulate. Early results were promising, as it accomplished both of these goals. The vaccine makes use of a live attenuated vrius that is administered as a nasal mist. Human trials are set to begin in 2014 and could be sumbitted to the FDA for approval as soon as 2019, which is a short time frame compared to that of other drug applications. FluGen anticipates patients needing a dose of their vaccine every three to five years to ensure protection against all strains, which is still less often than the yearly dosage recommended for current vaccines (Newman, 2013).

2003-2004 Influenza Season

The flu season of 2003-2004 was an important turning point in the history of influenza. It is not solely for the season's strain virulence, or the number of deaths that occurred, but because of how the U.S. began to handle this information. Many databases were started that season, including the Influenza Hospitalization Surveillance Network (FluSurv-NET) and the National Notifiable Diseases Surveillance System (Hall-Baker, et al., 2009).

One research goal of this paper was to find out which factors directly contributed to the large increase and subsequent elevation in early childhood (under five years of age) deaths due to influenza beginning with the 2003-2004 flu season. Specifically, from 2002 to 2003, this number increased from 12 to 90, and has remained high ever since at around 30-40 deaths annually. This increase in childhood deaths due to influenza can be seen in the first chart below and compared to overall deaths (see Figures 2 and 3), created from the CDC's annual

mortality reports. Concerns have been raised because this increase coincides with the ACIP's encouragement to vaccinate children aged 6-23 months against influenza beginning in the 2002-2003 flu season. They later upgraded this to a recommendation for the 2004-2005 flu season (Eisenberg, et al., 2008).

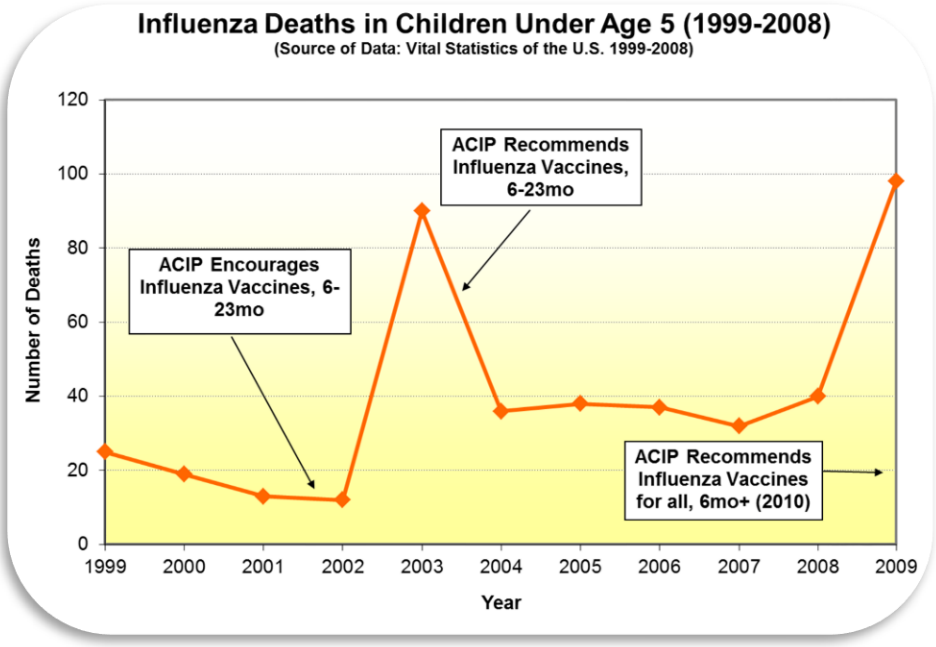



*Figure 2 – Influenza Deaths in Children Under Age 5 (1999-2008)*

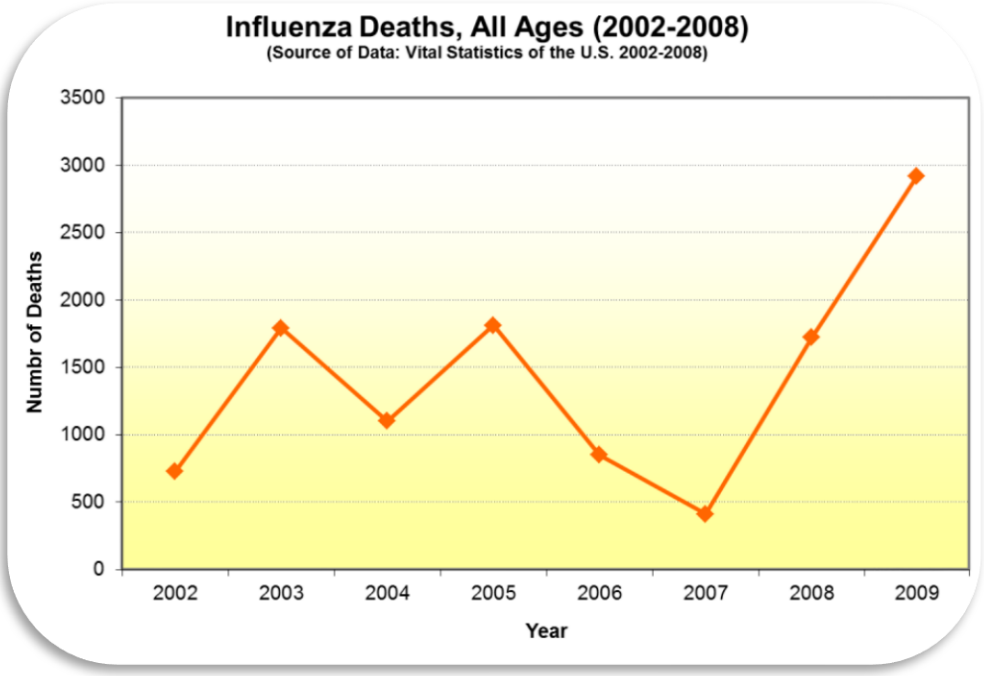



*Figure 3 – Influenza Deaths, All Ages (2002-2008)*

Overall, there were multiple causes behind the elevated death rate during this time. First of all, the vaccine was poorly matched to the actual strain of flu virus that prevailed in that season. The A (H3N2) subtype chosen for the flu vaccine based on past seasons was A/Panama/2007/99 (an A/Moscow/99 virus). This strain, however, was not the one that prevailed and sickened most people that year. Instead, it was A/Fujian/411/2002 that dominated, unfortunately not one of the strains in the vaccine. Late reports by WHO showed that virus isolates were different from A/Panama/2007/99 and closely related to A/Fujian/411/2002. Unfortunately, there was no virus similar to the latter strain that had been isolated in eggs, so the decision was made to include the next most promising strain, A/Panama/2007/99. Because of this mismatch, the vaccine lost a great deal of its potential effectiveness (Recommendations, 2003) (see Appendix B).

A study by Eisenberg et al. (2008) was conducted to discern the efficacy of the influenza vaccine in children aged 6-59 months during both the 2003-2004 and 2004-2005 flu seasons in more depth. Case studies were conducted on children who had tested positive for influenza, as well as control children who had tested negative. Demographic information was gleaned through patient records and parental interviews. It was determined that, in both years, there

was a "suboptimal" match between the circulating and vaccine influenza strains. Around 19% of the children in the study were fully vaccinated against influenza for both years. Statistical analysis showed that full vaccination was associated with "significantly fewer influenza-related inpatient, emergency department, or outpatient clinic visits in 2004–2005" and had an effectiveness of 57%. This was not the case in 2003-2004, however, in which the vaccine effectiveness was only 44%. In both years, partial vaccination was not effective (Eisenberg, et al., 2008). Although this study did not compare vaccination rates to death rates directly, the conclusion regarding the 2003-2004 vaccine supports the idea that it failed to adequately protect the recipients from influenza and subsequent deaths.

Secondly, the vaccination rate in children was still extremely low even after the encouragement to vaccinate. A study done by Santibanez et al. (2006) compared influenza vaccine rates in children aged 6 to 23 months during the 2002-2003 and 2003-2004 flu seasons using the National Immunization Survey. Two measures were included: those who had received one or more influenza vaccinations during September to December of the given flu season, and those who had been fully vaccinated (two doses if they had never been vaccinated against influenza before) between September and January. Demographics of each child's family were noted. As for the analysis, weighted adjustments were made to determine a national estimate, and statistical tests were run to search for any significance between influenza vaccination status and certain demographic and immunization-provider features. Results showed that during the 2002-2003 and 2003-2004 flu seasons, 7.4% and 17.5% (respectively) of children aged 6 to 23 months received at least one dose of influenza vaccine. It was also noted that, of these children, 40% and 52%, respectively, did not receive a second dose to be considered fully vaccinated. This means that vaccine coverage was fairly poor over both of the seasons, which may point to other causes of death besides the vaccines themselves. Disparities among demographics were found as well, highlighting lower maternal education, a large number of children per household, receiving vaccines at public clinics, and being of African American race as factors correlating with lower vaccination coverage (Santibanez, Santoli, Bridges, & Euler, 2006). The vaccine rate significantly increased after encouragement, but was still less than 20% (Hemingway & Poehling).

One study conducted by Bhat and Wright (2005) did specifically analyze characteristics of the children who died from the 2003-2004 flu, including their vaccination status. Of the 153 children under eighteen who passed away, the median age was three. For those younger than six months old, mortality rates were highest. 24% of 102 children tested positive for bacterial co-infections, while 33% had an underlying medical condition known to raise the chance of influenza-related complications. Only 16% or eighteen children who died of flu had been vaccinated with one dose of the flu vaccine. Of those, only eight had been fully vaccinated (Bhat, et al., 2005). Therefore, it is highly unlikely that there was any connection between the vaccine and the increase and deaths. The main cause, consequently, can be attributed to the virulence of the strain that year (A/H3N2) and the lack of antibodies present in the immature immune systems of children.

Interestingly, there were some regional discrepancies in the data reported by Bhat and Wright (2005). As seen below, almost half of all childhood influenza-related deaths occurred in the South. The other half was split between the West and Midwest, while the Northeast accounted for just 8% of deaths (see Figure 4).

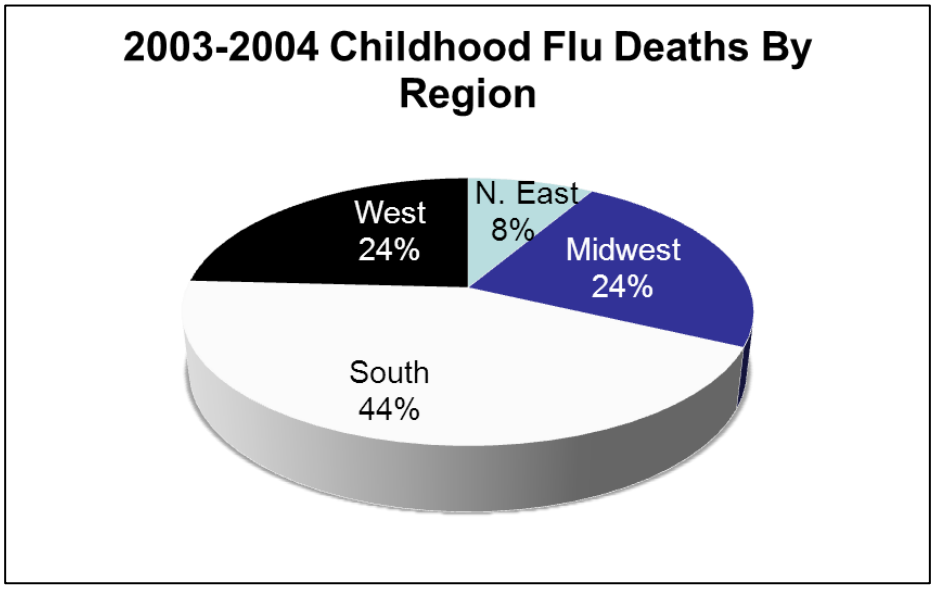



*Figure 4 – Regional Childhood Flu Deaths, 2003-2004*

## METHODOLOGY

Upon noticing the regional discrepancies in death tolls, this became a new area of interest to explore. Namely, were there in fact regional differences that are sustained over time, or was

this an anomaly? More importantly though, how effective is the flu vaccine in children? The first approach chosen to answer these questions was to compare childhood flu vaccine coverage rates and death rates due to flu in each state. Unfortunately, after searching the National Immunization Survey (NIS) database, CDC, and visiting the Rhode Island Department of Health, it was determined that there was not enough mortality data to effectively conduct this analysis. The following factors were to blame:

- Very few or no childhood deaths in some states (such as Rhode Island)
- Inconsistent age ranges between the two types of data
- Inconsistent regional groupings between the two groups of data
- Inconsistent time periods (some data was listed by year, while other data was categorized by flu season, which would yield two very different figures)

This led to the first change made to the type of data being used in the analysis. At the suggestion of analysts at the Rhode Island DOH, hospitalization rates due to influenza were used instead of death rates, since there would be much more to work with. However, this too soon proved futile. The only consistent, publically available vaccine coverage data available is from the NIS, which only measured the coverage rates in children aged 6 to 23 months until recently (2008), as mentioned previously. The hospitalization data found through Healthcare Cost and Utilization Project (HCUP), on the other hand, categorized children as 0-17 years of age in their statewide database, which was obviously too large of a span to compare to the vaccine coverage data. (It was not until 2010 that the CDC gathered and posted data for more current seasons using FluView as their medium, which listed young children as 6 months to 4 years of age.)

Once again, it was necessary to explore another measure of the flu's impact. This time, U.S. influenza-like illness (ILI) outpatient visits due to flu were used as this indicator. Specifically, this data came from regional ILI visits reported by ILI Surveillance Network (ILINet) providers. It was classified by Health and Human Services (HHS) regions of the U.S (see Appendix C). Unfortunately, NIS data for vaccine coverage was not consistent between seasons, and instead either provided counts by years rather than seasons or omitted flu vaccine

rates altogether. The only seasons with the necessary data available over the last decade were 2003-2004, 2009-2010, 2010-2011, and 2011-2012. Also, national vaccine coverage and outpatient rates for seven flu seasons (2002-2009) were compared in a final analysis.

For the first four regional analyses, data was gathered from both the NIS and ILINet. Although the NIS data was already in terms of a rate, the outpatient data on ILINet was not. In order to remedy this, it was deemed appropriate to create outpatient rates based on total regional populations. Unfortunately, these figures are not readily accessible since the U.S. Census does not split regional population by the same age range as the NIS. In order to estimate these numbers, the national percentage of 0-4 year olds in both the 2000 and 2010 censuses (6.81% and 6.50%, respectively) was multiplied by total regional populations for each of the ten regions (see Appendix D).

Next, the vaccine coverage rates by region were treated as the X variable, while the outpatient rates by region were treated as the Y variable for graphing purposes. Using Excel, the data points were plotted as a scatterplot on an X-Y axis, and a linear trendline was fitted to the ten data points for each of the four flu seasons. The same was done for the national rates over seven seasons (see Figures 5-9 and Appendix E).

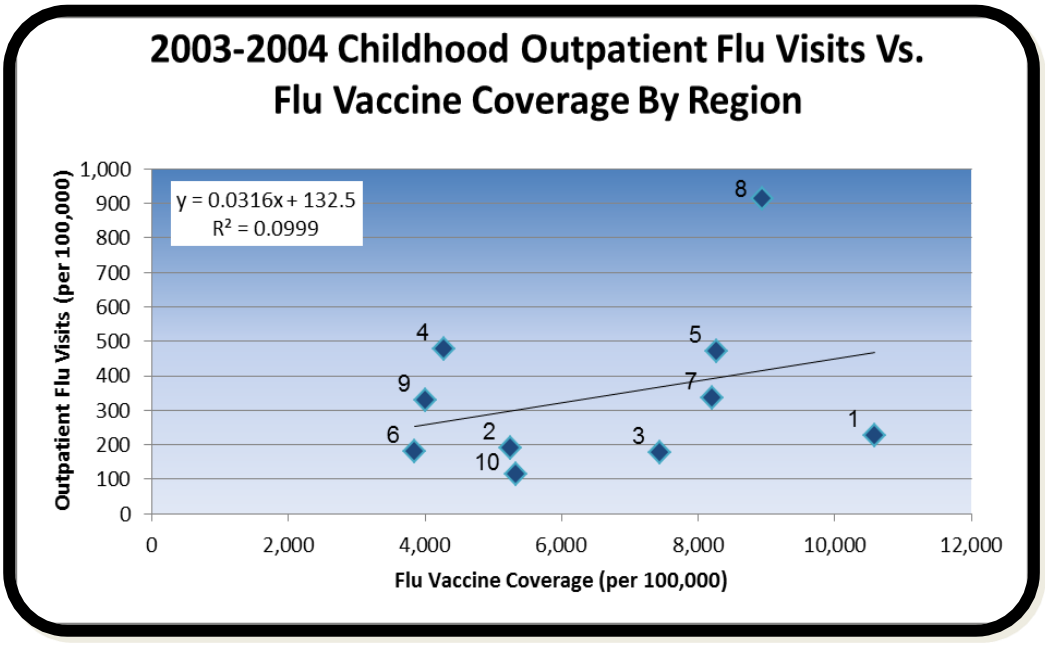



*Figure 5 – 2003-2004 Childhood Outpatient Flu Visits vs. Flu Vaccine Coverage By Region*

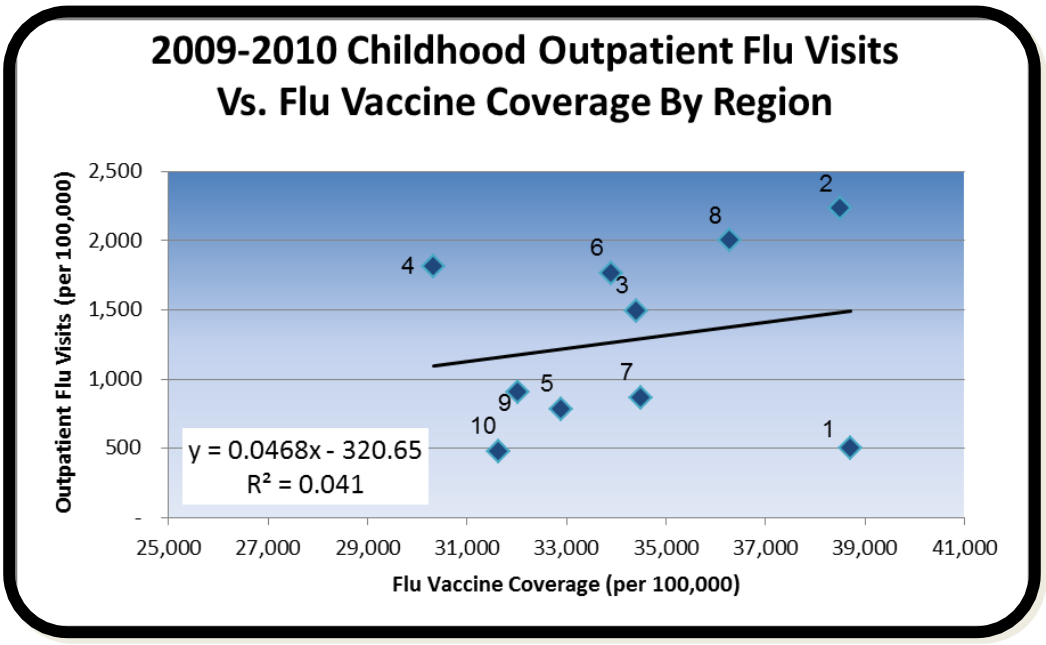



*Figure 6 – 2009-2010 Childhood Outpatient Flu Visits vs. Flu Vaccine Coverage By Region*

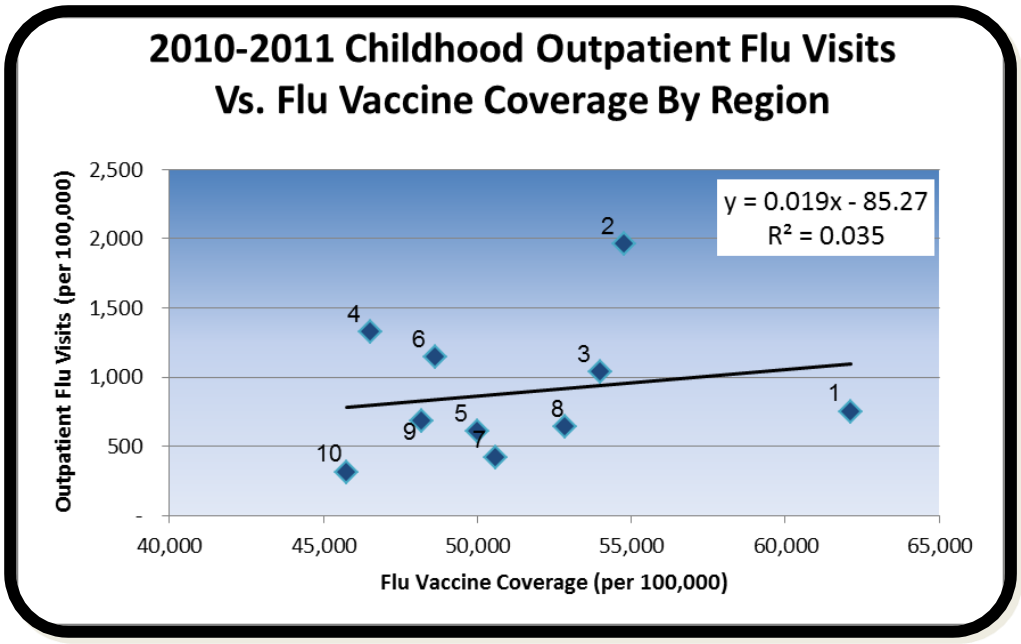



*Figure 7 – 2010-2011 Childhood Outpatient Flu Visits vs. Flu Vaccine Coverage By Region*

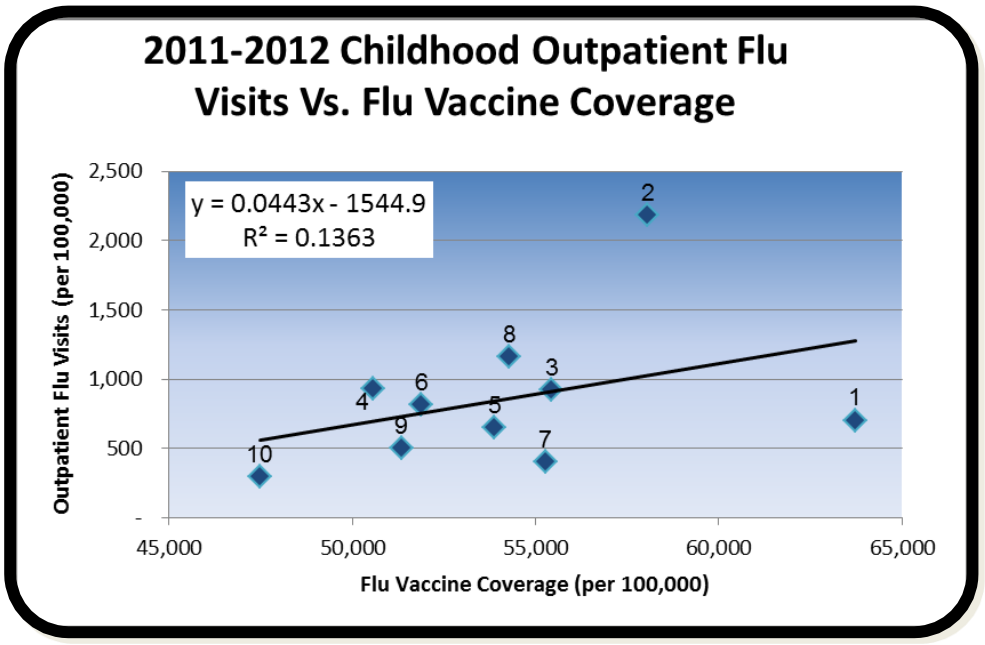



*Figure 8 – 2011-2012 Childhood Outpatient Flu Visits vs. Flu Vaccine Coverage By Region*

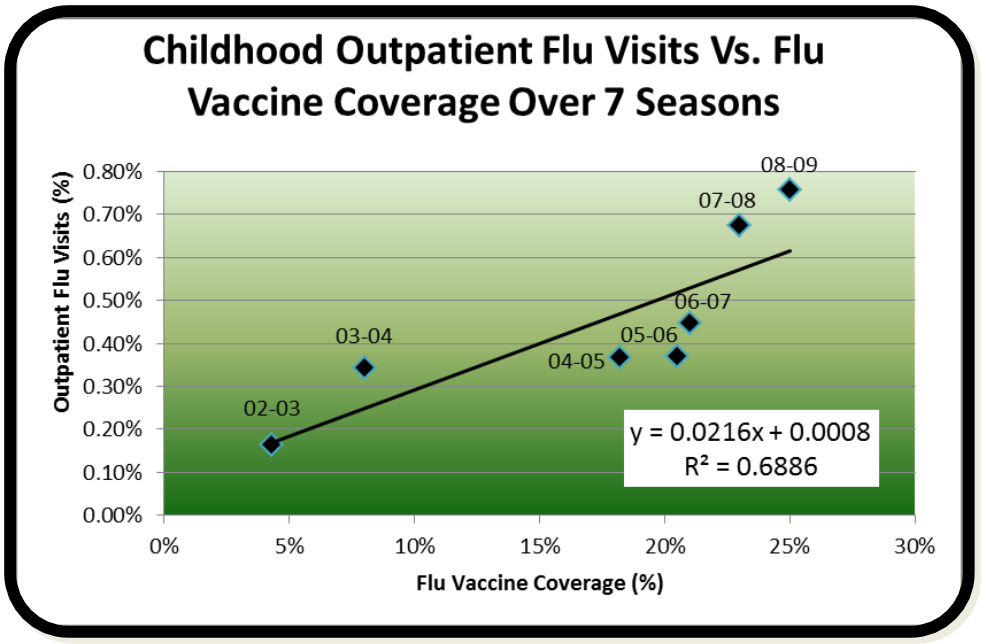



*Figure 9 –Childhood Outpatient Flu Visits vs. Flu Vaccine Coverage Over 7 Seasons*

Finally, a regression analysis was conducted on each set of data and tested for statistical significance using ANOVA. For each data set, the ANOVA hypotheses were as follows:

- $H_0$: The slope is equal to 0 (there is no relationship between childhood flu vaccine coverage rates and childhood ILI outpatient rates).
- $H_{A:}$ The slope is not equal to 0.

## RESULTS & DISCUSSION

The ANOVA results are summarized in Figure 10 below:

| Year | F-Value | P-Value | Significance (alpha=0.05) |
|---|---|---|---|
| **2003-2004** | 0.882 | 0.37 | Not significant (>0.05) |
| **2009-2010** | 0.342 | 0.57 | Not significant (>0.05) |
| **2010-2011** | 0.289 | 0.61 | Not significant (>0.05) |
| **2011-2012** | 1.263 | 0.29 | Not significant (>0.05) |
| **7 Seasons** | 11.054 | 0.02 | Significant (<0.05) |

*Figure 10 – Results Summary*

Looking at the $R^2$ correlation coefficients for each graph is very telling of the relationship strength in each year. The first four graphs all have very low correlation coefficients (close to 0), meaning that there is no significant relationship between flu vaccine coverage and outpatient rates (confirmed by the regression analysis and ANOVA test of significance).

Upon doing this initial analysis, the graphs were fit to other models in Excel to test whether or not this would increase the $R^2$. Sure enough, all of the correlations improved a great deal. The season that showed the most improvement with a higher-order model was 2010-2011, which was fit to a $6^{th}$ degree polynomial trendline (see Figure 11).

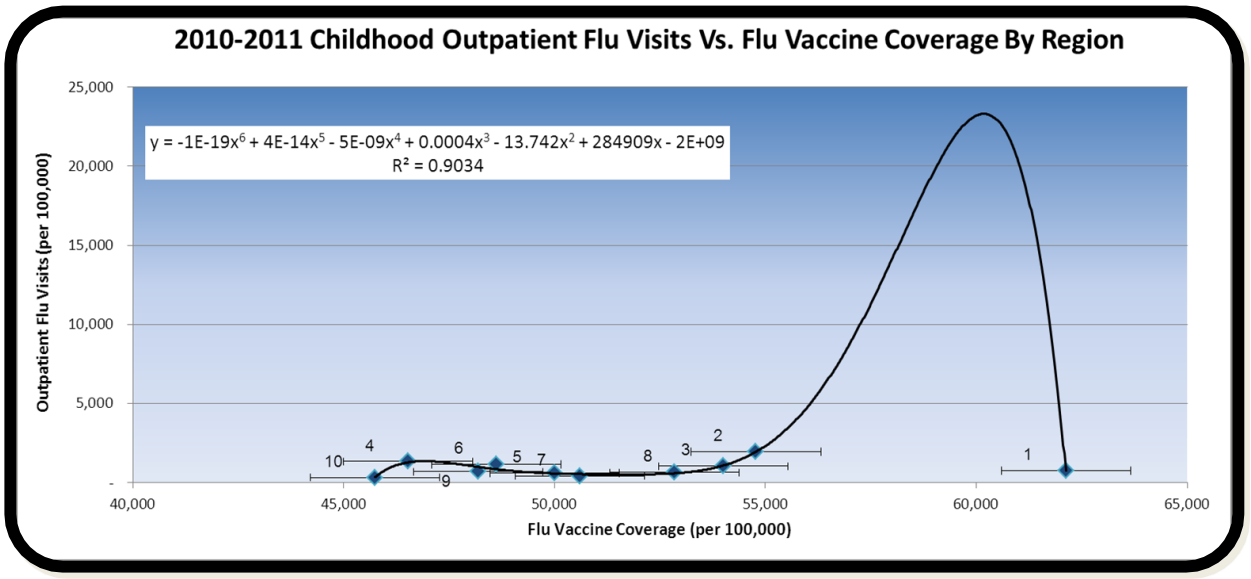



*Figure 11 – Revised Trendline for 2010-2011*

This reveals that the relationship between vaccination rates and outpatient rates is not strictly linear, and may not be a direct relationship. Instead, there may very well be other factors or variables influencing the relationship (see Figure 12). These could potentially include the overall health and population density of each region. For example, it has been shown in a study by Cullen, Cummins, & Fuchs (2012) that geographic disparities among life expectancies do exist. Even after adjusting for racial distribution, they are still very significant (though there is an additional link between race and life expectancy). The South and heavily urban areas have the lowest probabilities of survival to age 70 for all races, though only white males are shown (see Figure 13) (Cullens, Cummins, & Fuchs, 2012). This could explain one anomaly that exists in Region 2 – New York and Region 3 - Philadelphia. For the last three seasons in the analysis (2009-2012), both New York and Philadelphia consistently reported above-average outpatient rates, yet also achieved above-average vaccination rates. The higher population density and urban atmosphere could be in effect here.

Two other potential variables are the region's attitude towards vaccines, as well as their accessibility. For example, it could be theorized that because the overall well-being of people in the South is lower than average, people are less health-conscious. They may not be aware of all the potential benefits of vaccines, or they may simply be closed-minded to them. This could explain the low vaccination coverage rate in the South over all flu seasons. As far as

accessibility, one example of its effect on vaccine coverage rates is seen in Region 5 – Chicago. In three out of the four seasons individually analyzed, Chicago reported lower than average vaccination rates, yet also had below-average outpatient rates due to flu. Perhaps this area's vaccination programs for children are not as strong as in the Northeast, which has vaccination clinics within schools. Also, the harsh winter weather in the northern area of Region 5 may be responsible for decreased accessibility to flu vaccines.

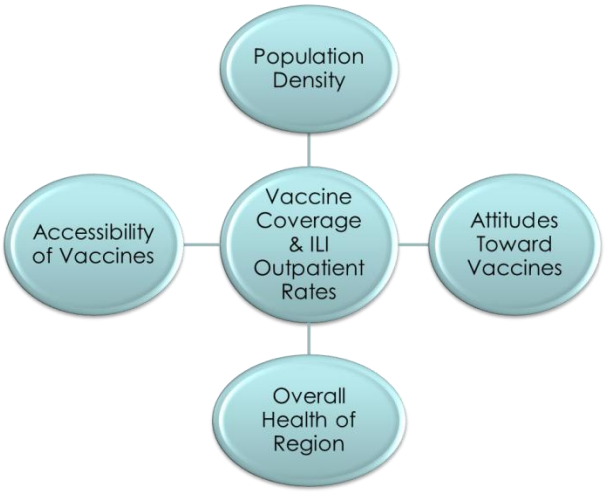



*Figure 12 – Potential Factors Influencing Vaccine Coverage/Outpatient Rate Relationship*

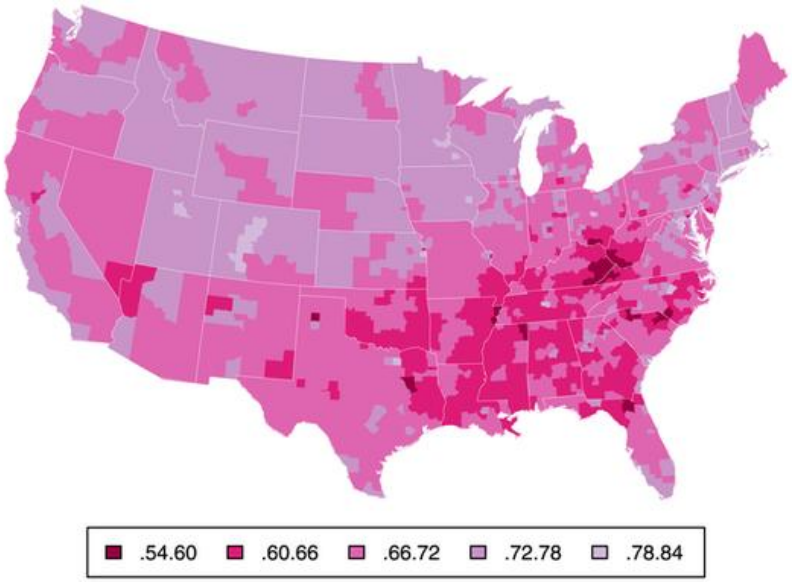



*Figure 13 - Probability of Survival to Age 70 for White Males*
*Source: (Cullen, Cummins, & Fuchs, 2012)*

On the other hand, the graph of national rates over seven seasons reveals a moderately strong linear relationship with a correlation of 69% and is statistically significant (p=0.02). In other words, as childhood flu vaccination coverage rates increase, so do childhood ILI outpatient rates. At first thought, this trend seems counter-intuitive. Upon further inspection, it is apparent that confounding factors may also exist. Here again, the correlation coefficient increased when the data was fit to a high-order polynomial model, which supports this line of thought (see Figure 14).

It may be that increased health awareness overall is causing this seemingly baffling relationship. The two sub-factors that contribute to this increased awareness are higher vaccination rates and higher outpatient visits (the two variables being studied). Taking it one step further, two factors that lead to more doctor visits are improved accessibility of clinics and more self-diagnosis tools and inclinations. The advent of walk-in clinics and convenience of these facilities compared to doctors' offices (i.e., closer distance, longer hours) could very well be a cause of increased outpatient visits. People are more likely to see a doctor when they feel symptoms of the flu since it is much easier now than it once was. In addition, this generation may have a more favorable attitude of doctors and taking advantage of the help they offer, being more health conscious and aware of the media that supports this view. Finally, self-diagnosis via the Internet may be another factor contributing to increased outpatient visits. It is very easy for a parent to search their child's symptoms online and become concerned. Ultimately, they decide that these symptoms warrant a doctor visit. All of these factors should not necessarily be viewed in a negative or positive light, but may simply help explain why childhood ILI outpatient rates increase with flu vaccine coverage rates.

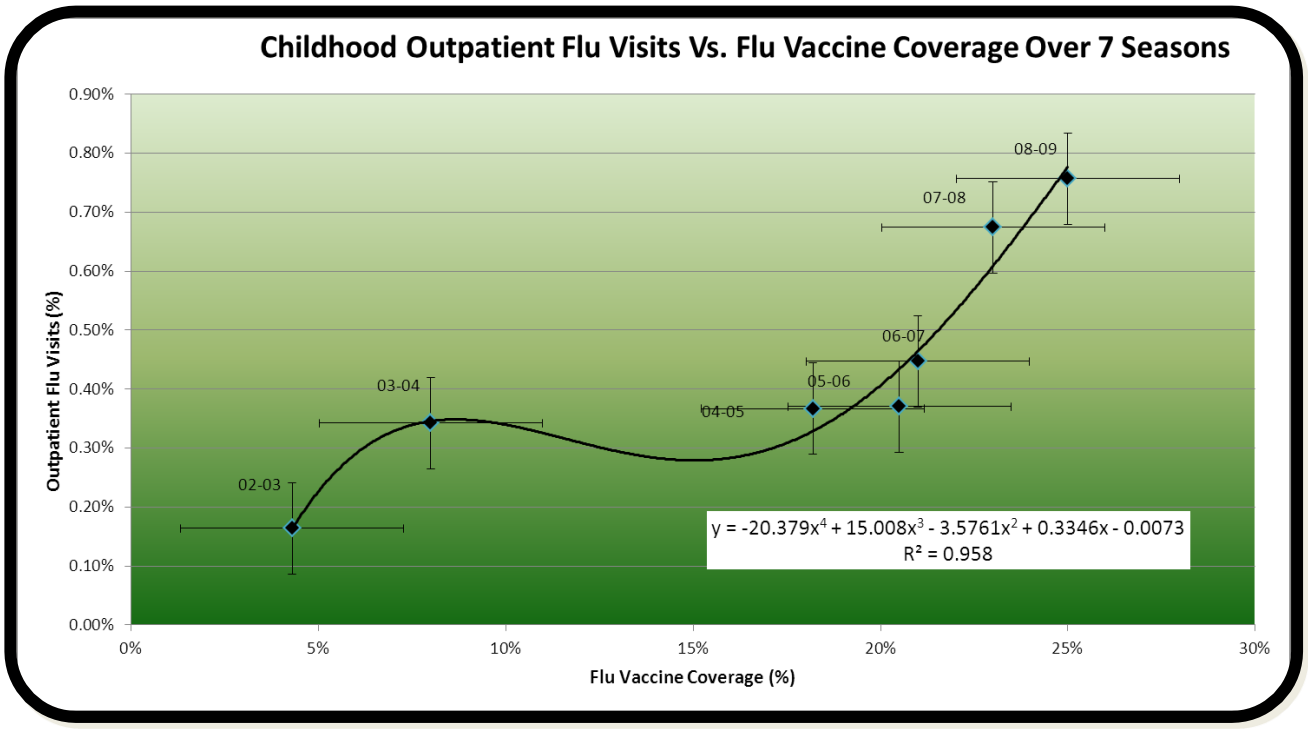



*Figure 13 - Probability of Survival to Age 70 for White Males*

## LIMITATIONS

One main limitation lies in the fact that, although the most consistent data was chosen, the age range of the flu vaccine coverage data was 6-23 months of age for some years, while the outpatient data was from 0-4 years of age. During the swine flu pandemic, the coverage rates were only measured for a larger group of children aged 6 months to 17 years of age. Finally, from 2010-2012, the coverage rates were the most similar to the hospitalization rates, the former age range being from 6 months to 4 years of age.

Another limitation is the way in which regional population was calculated in order to transform outpatient figures into rates. Because the U.S. Census does not break down regional population by age increments as small as 0-4 years of age, this had to be estimated based on the national figures. This assumes that the national distribution is the same throughout the country, but this may not necessarily be the case.

## CONCLUSION & NEXT STEPS

The conclusion of this capstone is not meant to be a definitive answer on whether or not influenza vaccines are effective, or even the extent to which they are so. Rather, the emphasis should be on the fact that there was no direct, linear relationship between childhood influenza vaccination rates and childhood ILI outpatient rates. There is potential for expanded studies on what confounding factors may be contributing to this relationship. On the other hand, although national flu vaccination and outpatient rates in children did reveal a positive, significant relationship, this also must be examined below the surface for additional factors. It is too easy to fall into the trap of taking data at face value, such as when it is presented by the media.

The many obstacles faced throughout this capstone regarding data accessibility and presentation underscores the need for enhanced public health communications. It is crucial that parents have the necessary information to make informed immunization decisions for both themselves and their children. Thus, further analysis is called for in order to present a clear picture to the public. With health awareness on the rise, there is a great yearning for this void to be filled.

# APPENDICES

Appendix A – Influenza Manufacturers

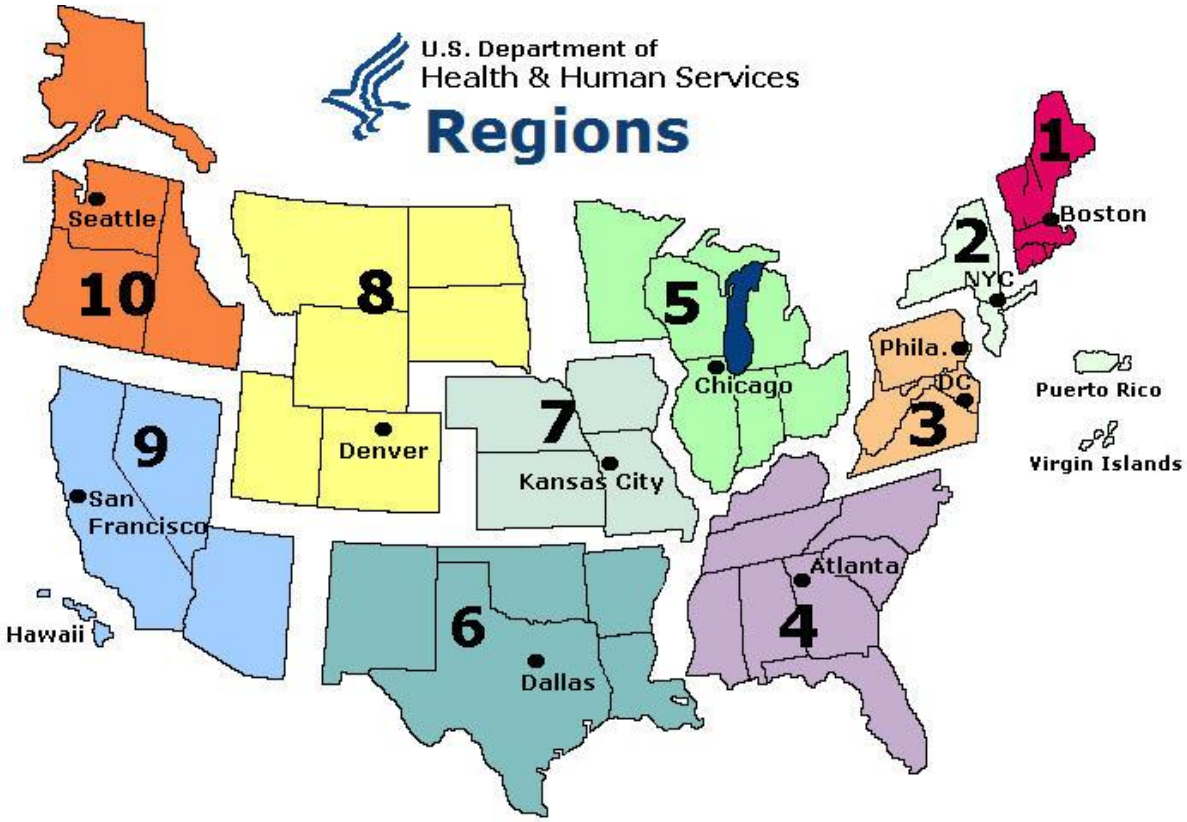
## Influenza Vaccine Information for the 2012-2013 Flu Season

| Vaccine | Trade Name | Manufacturer |
|---|---|---|
| TIV | Fluzone | Sanofi Pasteur |
| TIV | Agriflu | Novartis Vaccines |
| TIV | Fluvirin | Novartis Vaccines |
| | | |
| TIV | Fluarix | GlaxoSmithKline |
| TIV | FluLaval | ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline) |
| TIV | Afluria | CSL Biotherapies (distributed by Merck) |
| TIV high-dose | Fluzone High-Dose | Sanofi Pasteur |
| TIV intradermal | Fluzone Intradermal | Sanofi Pasteur |
| LAIV | FluMist | MedImmune |

Appendix B – Influenza Vaccine Virus Strains By Season

| INFLUENZA VACCINE VIRUS STRAINS BY SEASON | | | |
|---|---|---|---|
| **Season** | **A(H1N1)** | **A(H3N2)** | **Type B** |
| 02–03 | A/New Caledonia/99 | A/Panama/2007/99 (A/Moscow/10/99-like virus) | B/Hong Kong/2001 |
| 03–04 | A/New Caledonia/99 | A/Panama/2007/99 (A/Moscow/10/99-like virus) | B/Hong Kong/2001 |
| 04–05 | A/New Caledonia/99 | A/Fujian/2002 | B/Shanghai/2002 |
| 05–06 | A/New Caledonia/99 | A/California/2004 | B/Shanghai/2002 |
| 06–07 | A/New Caledonia/99 | A/Wisconsin/2005 | B/Malaysia/2004 |
| 07–08 | A/Solomon Islands/06 | A/Wisconsin/2005 | B/Malaysia/2004 |
| 08–09 | A/Brisbane/2007 | A/Brisbane/2007 | B/Florida/2006 |
| 09–10 | A/Brisbane/2007 | A/Brisbane/2007 | B/Brisbane/2008 |
| 10–11 | A/California/2009* | A/Perth/2009 | B/Brisbane/2008 |
| 11–12 | A/California/2009* | A/Perth/2009 | B/Brisbane/2008 |
| 12–13 | A/California/2009* | A/Victoria/2011 | B/Wisconsin/2010 |
| *2009 swine flu (H1N1) pandemic strain<br>Source: FDA Lot Release | | | |

Appendix C – HHS Regions



Appendix D – Calculation of Regional Populations for Age 0-4

| | Regional Population 2000 | Regional Population 2010 | 0-4 y.o. Population 2000 | 0-4 y.o. Population 2010 |
|---|---|---|---|---|
| **Region 1 - Boston** | 13,922,517 | 14,444,865 | 948,665.93 | 938,916.23 |
| **Region 2 - New York** | 27,390,807 | 28,169,996 | 1,866,381.30 | 1,831,049.74 |
| **Region 3 - Philadelphia** | 27,820,058 | 29,829,606 | 1,895,630.02 | 1,938,924.39 |
| **Region 4 - Atlanta** | 53,252,966 | 61,082,315 | 3,628,602.10 | 3,970,350.48 |
| **Region 5 - Chicago** | 50,074,516 | 51,725,489 | 3,412,025.80 | 3,362,156.79 |
| **Region 6 - Dallas** | 33,263,896 | 38,405,381 | 2,266,567.52 | 2,496,349.77 |
| **Region 7 - Kansas City** | 12,921,216 | 13,714,741 | 880,438.31 | 891,458.17 |
| **Region 8 - Denver** | 9,327,451 | 10,832,893 | 635,562.88 | 704,138.05 |
| **Region 9 - San Francisco** | 42,212,074 | 47,706,825 | 2,876,287.12 | 3,100,943.63 |
| **Region 10 - Seattle** | 11,236,405 | 12,833,427 | 765,637.03 | 834,172.76 |
| | **281,421,906** | **308,745,538** | **19,175,798.00** | **20,068,459.97** |
| | | Percent of 0-4 yr olds in the US, **6.81%** | Percent of 0-4 yr olds in the US, 2010: **6.50%** | |

## Appendix E – Data

Note:

Green=low outpatient, high vaccination coverage (based on whether it was above or below average)

Red=high outpatient, low vaccination coverage (based on whether it was above or below average)

2003-2004

| Region | Childhood Full Dose Flu Vaccine Coverage Per 100,000* | Childhood Outpatient ILI Visits Per 100,000** |
|---|---|---|
| Region 1 - Boston | 10,583.33 | 225.90 |
| Region 2 - New York | 5,250.00 | 190.26 |
| Region 3 - Philadelphia | 7,433.33 | 175.88 |
| Region 4 - Atlanta | 4,275.00 | 477.90 |
| Region 5 - Chicago | 8,266.67 | 470.86 |
| Region 6 - Dallas | 3,840.00 | 180.67 |
| Region 7 - Kansas City | 8,200.00 | 334.95 |
| Region 8 - Denver | 8,933.33 | 914.46 |
| Region 9 - San Francisc | 4,000.00 | 328.76 |
| Region 10 - Seattle | 5,325.00 | 113.89 |
| AVERAGE | **6,610.67** | **341.35** |

*6-23mo

**0-4yo

2009-2010

| Region | Childhood Full Dose Flu Vaccine Coverage Per 100,000* | Childhood Outpatient ILI Visits Per 100,000** |
|---|---|---|
| Region 1 - Boston | 38,700.00 | 502.92 |
| Region 2 - New York | 38,500.00 | 2,233.20 |
| Region 3 - Philadelphia | 34,400.00 | 1,495.39 |
| Region 4 - Atlanta | 30,323.18 | 1,810.95 |
| Region 5 - Chicago | 32,884.54 | 781.50 |
| Region 6 - Dallas | 33,897.26 | 1,767.56 |
| Region 7 - Kansas City | 34,506.17 | 866.50 |
| Region 8 - Denver | 36,279.52 | 1,999.96 |
| Region 9 - San Francisc | 32,030.71 | 906.59 |
| Region 10 - Seattle | 31,633.07 | 477.51 |
| AVERAGE | **34,315.45** | **1,284.21** |

*6m-17yo

**0-4yo

2010-2011

| Region | Childhood Full Dose Flu Vaccine Coverage Per 100,000* | Childhood Outpatient ILI Visits Per 100,000** |
|---|---|---|
| Region 1 - Boston | 62,123.08 | 752.25 |
| Region 2 - New York | 54,778.57 | 1,958.77 |
| Region 3 - Philadelphia | 54,010.29 | 1,037.28 |
| Region 4 - Atlanta | 46,524.71 | 1,326.81 |
| Region 5 - Chicago | 50,007.69 | 609.52 |
| Region 6 - Dallas | 48,628.57 | 1,144.71 |
| Region 7 - Kansas City | 50,595.74 | 418.42 |
| Region 8 - Denver | 52,845.31 | 639.79 |
| Region 9 - San Francisc | 48,197.87 | 682.08 |
| Region 10 - Seattle | 45,742.55 | 314.44 |
| AVERAGE | **51,345.44** | **888.41** |

*6m-4yo

**0-4yo

2011-2012

| Region | Childhood Full Dose Flu Vaccine Coverage Per 100,000* | Childhood Outpatient ILI Visits Per 100,000** |
|---|---|---|
| Region 1 - Boston | 63,717.19 | 700.38 |
| Region 2 - New York | 58,051.72 | 2,184.43 |
| Region 3 - Philadelphia | 55,436.92 | 921.18 |
| Region 4 - Atlanta | 50,580.00 | 930.95 |
| Region 5 - Chicago | 53,873.13 | 649.55 |
| Region 6 - Dallas | 51,887.50 | 813.03 |
| Region 7 - Kansas City | 55,273.33 | 401.48 |
| Region 8 - Denver | 54,284.62 | 1,161.42 |
| Region 9 - San Francisc | 51,336.17 | 498.04 |
| Region 10 - Seattle | 47,476.60 | 290.83 |
| AVERAGE | **54,191.72** | **855.13** |

*6m-4yo

**0-4yo

| Overall | | |
|---|---|---|
| **Year** | **Childhood Full Dose Flu Vaccine Coverage Estimates (%)*** | **National Childhood Outpatient ILI Visits (%)**** |
| 02-03 | 4.30% | 0.16% |
| 03-04 | 8.00% | 0.34% |
| 04-05 | 18.20% | 0.37% |
| 05-06 | 20.50% | 0.37% |
| 06-07 | 21.00% | 0.45% |
| 07-08 | 23.00% | 0.67% |
| 08-09 | 25.00% | 0.76% |
| AVERAGE | **17.14%** | **0.45%** |
| *6-23mo | | |
| **0-4yo | | |

# REFERENCES

(2008). *Understanding Vaccines: What They Are and How They Work.* National Institutes of Health. National Institute of Allergy and Infectious Diseases.

*Antigenic Drift*. (2011, January 14). Retrieved from National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov/topics/Flu/Research/basic/Pages/AntigenicDriftIllustration.aspx

*Antigenic Shift*. (2011, January 14). Retrieved from National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov/topics/Flu/Research/basic/pages/AntigenicShiftIllustration.aspx

Bhat, N., Wright, J. G., Broder, K. R., Murray, E. L., Greenberg, M. E., Glover, M. J., . . . Uyeki, T. M. (2005). Influenza-Associated Deaths among Children. *The New England Journal of Medicine*.

Chang, H. J. (2011). Influenza. *JAMA: The Journal of the American Medical Association*.

Cullens, M. R., Cummins, C., & Fuchs, V. R. (2012). Geographic and Racial Variation in Premature Mortality in the U.S.: Analyzing the Disparities. *PLoS ONE, 7*(4).

Eisenberg, K. W., Szilagyi, P. G., Fairbrother, G., Griffin, M. R., Staat, M., Shone, L. P., . . . Iwane, M. K. (2008). Vaccine Effectiveness Against Laboratory-Confirmed Influenza in Children 6 to 59 Months of Age During the 2003-2004 and 2004-2005 Influenza Seasons. *Pediatrics, 122*(5), 911-919.

*Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu*. (2011, June 24). Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm

*Flu Overview*. (2012, November 16). Retrieved from National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov/topics/Flu/understandingFlu/Pages/overview.aspx

*Fluzone High-Dose Seasonal Influenza Vaccine*. (2012, July 16). Retrieved from Seasonal Influenza (Flu): http://www.cdc.gov/flu/protect/vaccine/qa_fluzone.htm#does_cdc

Folkers, G. K., Morens, D. M., & Fauci, A. S. (2009). What is a Pandemic. *Journal of Infectious Diseases*, 1018-1021.

Hall-Baker, P. A., Nieves, E., Jajosky, R., Adams, D. A., Sharp, P., Anderson, W. J., . . . Rey, A. (2009). *Summary of Notifiable Diseases --- United States, 2007.* Morbidity and

Mortality Weekly Report. Center for Disease Control and Prevention. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5653a1.htm

*Influenza (Seasonal)*. (2009, April). Retrieved from World Health Organization: http://www.who.int.revproxy.brown.edu/mediacentre/factsheets/fs211/en/index.html

Janeway, C. A., & Travers, P. (1996). *Immunobiology: The Immune System in Health and Disease.* London; San Francisco: New York: Current Biology; Garland Pub.

*Key Facts About Seasonal Flu Vaccine*. (2013, January 16). Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/flu/protect/keyfacts.htm

Kroger, A. T., Sumaya, C. V., Pickering , L. K., & Atkinson, W. L. (2011, January 28). *General Recommendations on Immunization.* Retrieved from Morbidity and Mortality Weekly Report (MMWR): http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm?s_cid=rr6002a1_e

*Lot Release (Biologics): Influenza Virus Vaccine Composition and Lot Release*. (2013, March 15). Retrieved from U.S. Food and Drug Administration: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm062928.htm

Merino, N. (2010). *Should vaccinations be mandatory?* Detroit: Greenhaven Press.

Miller, N. Z. (2002). *Vaccines : are they really safe and effective?* Santa Fe: New Atlantean press.

Multidimensional Scaling; New way of predicting dominant seasonal flu strain. (2010, December 4). *Marketing Weekly News* .

*New Vaccine Technologies*. (2011, January 14). Retrieved from National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov/topics/Flu/Research/vaccineResearch/pages/technologies.aspx

Newman, J. (2013, February 9). Flugen works on universal vaccine. *Wisconsin State Journal*, D1.

*NIH Scientists Advance Universal Flu Vaccine.* (2010, July 15). Retrieved from NIH News (NIAID): http://www.niaid.nih.gov/news/newsreleases/2010/Pages/universalfluvax.aspx

*Optimizing Vaccines and Vaccine Production*. (2011, January 14). Retrieved from National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov/topics/Flu/Research/vaccineResearch/Pages/OptimizingVaccinesandVaccineProduction.aspx

Osterholm, M. T., Kelley, N. S., Sommer, A., & Belongia, E. A. (2012, January). Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *The Lancet Infectious Diseases, 12*(1), 36-44. doi:10.1016/S1473-3099(11)70295-X

*Pandemic (H1N1) 2009*. (2010, May 14). Retrieved from World Health Organization: http://www.who.int.revproxy.brown.edu/csr/don/2010_05_14/en/index.html

*People at High Risk of Developing Flu–Related Complications*. (2012, November 12). Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/flu/about/disease/high_risk.htm

Plotkin, S. L., & Plotkin, S. A. (2008). A short history of vaccination. In S. A. Plotkin, W. A. Orenstein , & P. A. Offit, *Vaccines* (pp. 6-7). Elseviewer Health Services.

*Recommendations for Influenza Vaccine Composition*. (2003). Retrieved from World Health Organization: Global Alert & Response: http://apps.who.int/csr/disease/influenza/vaccinerecommendations1/en/index13.html

Santibanez, T. A., Santoli, J. M., Bridges, C. B., & Euler, G. L. (2006). Influenza Vaccination Coverage of Children Aged 6 to 23 Months: The 2002-2003 and 2003-2004 Influenza Seasons. *Pediatrics*. doi:10.1542/peds.2006-0831

*Seasonal Influenza Vaccine Supply for the U.S. 2012-13 Influenza Season*. (2013, January 15). Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/flu/about/qa/vaxsupply.htm#table

*Selecting the Viruses in the Seasonal Influenza (Flu) Vaccine*. (2011, March 9). Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/flu/professionals/vaccination/virusqa.htm#other-factors

*Thimerosal and 2012-2013 Seasonal Flu Vaccines*. (2012, August 22). Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/flu/protect/vaccine/thimerosal.htm

*Types of Influenza Viruses*. (2012, March 22). Retrieved from Centers for Diseason Control and Prevention: http://www.cdc.gov/flu/about/viruses/types.htm

Walsh, B. (2009). A Brief History Of: Flu Pandemics. *Time Magazine*.

Wright, P. F., Thompson, J., & Karzon, D. T. (1980). Differing Virulence of H1N1 and H3N2 Influenza Strains. *American Journal of Epidemiology*.

*United States Surveillance Data*. (2010, March 23). Retrieved from CDC - Seasonal Influenza: http://www.cdc.gov/flu/weekly/ussurvdata.htm