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Cost-Benefit Analysis Of Universal Influenza Vaccination Programs: A Historical-Perspective Case Study Of Vermont

Bryan Charles O'Connor
University of Vermont

COST-BENEFIT ANALYSIS OF UNIVERSIAL INFLUENZA VACCINATION PROGRAMS: A HISTORICAL-PERSPECTIVE CASE STUDY OF VERMONT

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Bryan C. O'Connor

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Thesis Examination Committee:

Christopher Koliba, Ph.D.., Advisor
Christopher Jones, Ph.D., Chairperson
Josh Farley, Ph.D.
Cynthia J. Forehand, Ph.D., Dean of the Graduate College

ABSTRACT

Since 2010 the Center for Disease Control (CDC) and its Advisory Committee on Immunization Practices (ACIP) have recommended annual influenza vaccinations for all persons aged six months and up (ACIP, 2017). In December of the same year, the Agency of Health and Human Services (AHHS) unveiled *Healthy People 2020*, a series of health indicators and corresponding 10-year objectives. This newest iteration of the Healthy People program set target influenza vaccination levels for healthy adults 18 and older at 80% (AHHS, 2010).

Aside from the inherent health benefits, multiple studies conducted over the past decade suggest there may be significant economic benefits to a highly-vaccinated population. Depending on the effectiveness of seasonal vaccines, the cost of vaccinating a U.S. adult can be outweighed by the health care savings from the resulting reduction in direct and indirect infection treatment costs.

As the state of Vermont considers including influenza vaccinations in its state-mandated Vermont Vaccine Purchasing Program (VVPP), it presents a unique opportunity to conduct a state-wide case study on the potential cost-saving implications of a universally available influenza vaccination.

This study takes a historical perspective and looks back at Vermont's influenza cost, usage, and treatment information since the vaccine was recommended in 2010. Using data generated from Vermont's immunization registry, de-identified claims data, CDC-reported statistics, and numerous published economic studies, this research answers the question: "What societal costs/savings would have been witnessed if the influenza vaccine was included in the VVPP since 2010?" and, more important, what policy changes can be made now to realize savings in the future?

Using a dynamic transmission model embedded in cost-benefit analysis, this research concludes that influenza-related savings of 6.2% would have been experienced over the five flu seasons between fall 2010 and summer 2015. Most of the savings are generated by the increased vaccination rate associated with a universal vaccination program. Creation of such a program in the state of Vermont would likely be economically beneficial.

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INTRODUCTION

Between 5% and 25% of the global population can become infected with the influenza virus in any given year. Annually, hundreds of thousands are hospitalized by the pathogen; tens of thousands die. The morbidity and mortality associated with influenza can be mitigated by vaccination. Since 2010 the CDC has recommended all individuals aged 6 months and older receive an annual flu vaccine. Historically, the vaccine has been suggested for only populations at high risk of complication or transmission – children, the elderly, and healthcare workers. Only recently have working adults been recognized as vectors of the disease, acting as a bridge between other age groups. Only about 40% of working-age adults receive a flu vaccination each year.

This thesis will assess the costs and benefits of a universal vaccination program in the state of Vermont. An economic analysis of an epidemiological intervention is necessarily multidisciplinary. This paper includes considerations of economics and epidemiology in both its literature review and methods. It also includes information on the virus, its vaccine, and the public health mechanisms through which a universal vaccination program would be implemented.

This study is multidisciplinary in its nature, drawing on concepts from epidemiology, economics, and statistics. The literature review in this thesis will cover influenza, vaccinations, epidemiological models, economic models, existing universal vaccination programs, historic trends, and an overview of the data sources used.

The model itself is unique. Typically, vaccine program cost-benefit analysis and cost-effectiveness analysis measure the costs of vaccination against the cost of treatment. In the case of this research, I compare the total historic societal cost of influenza vaccination and treatment to what that cost would have been if there was a universal vaccination program. This model improves upon prior research by embedding a dynamic transmission model within a 5-year cost-benefit model covering the entire state of Vermont. The distinct combination of scale, time, and epidemiological factors accounts for the variable nuances of influenza vaccination in a way previous research has not. The methods section of this thesis includes details on the transmission model used, information on how the historic variables were collected, and how those variables were adjusted for inclusion in the intervention – a universal influenza vaccination program.

Finally, this paper discusses the results and limitations of the model, as well as a discussion section which addresses the implications of the findings. In the end, this research concludes that increased vaccination rates among adults aged 18-64 is economically beneficial, and recommends that a universal influenza program be implemented in Vermont and supported by the state-mandated Vaccine Purchasing Program.

CHAPTER 1: LITERATURE REVIEW

The research, analysis, and discussion included in this paper draw from a wide range of socioeconomic models and literature. The focal point of this project is an epidemiological model embedded within a cost analysis model – which is contextualized by the State of Vermont's public health climate. The literature reviewed must then support each of these components and included information on influenza, vaccinations, public health, economics, and infectious disease modeling.

1.1. Influenza

The influenza virus is a consistent, annual, and mitigatable public health risk that affects large portions of the U.S. population every year. This research deals only with inter-pandemic, or "seasonal" influenza. Seasonal influenza epidemics typically peak in the late fall through early spring and affect individuals across all demographics (ACIP, 2011; Lagacé-Wiens, 2010). Influenza epidemics vary widely in severity. The true number of infected individuals is difficult to know. The range of infected individuals has been identified as 1% to 26% (Bridges, 2000) and 5% to 20% (Kryscio, 2010). On average, influenza results in 36,000 deaths per year, with an additional 200,000 hospitalizations (Maciosek, 2006; Kryscio 2010). Death and serious illness is most common among children, the elderly, and pregnant women. The increase in mortality is largely due to pneumonia and influenza, but additional deaths are caused by exacerbated chronic illnesses in the respiratory and circulatory systems (Cox, 2000). Since 2010, the CDC's Advisory Committee on Immunization Practices has recommended "routine

annual influenza vaccination for all persons aged ≥6 months who do not have contraindications" (ACIP, 2017, p.2).

Influenza refers to a group of three segmented RNA genome viruses called orthomyxoviruses. The virus has threatened populations for thousands of years with possible pandemics occurring in ancient history – Hippocrates wrote about the spread of illnesses as early as 412 B.C. In 1891, the germ associated with influenza was named *Bacillus influenzae* by Pfeiffer, but the flu was recognized as a pathogen a year earlier. In 1933, Wilson Smith, Christopher Andrews, and Patrick Laidlow at the National Institute of Medicine "discovered" influenza as a virus during research on the pathogen's development. Soon after, in 1936 the first influenza vaccinations were created from inactivated viruses replicated in mice cells and then in the embryo of a hen (Kuszewski, 2000).

The viruses are typically identified as A, B, and C (Lagacé-Wiens, 2010; Cox, 2000). Of these three viruses, A and B are associated with seasonal morbidity, mortality and economic losses (Cox, 2000). Influenza A and B viruses were first isolated in 1933 and 1940, respectively. Influenza A is responsible for the majority of seasonal flu outbreaks and all epidemics (Lagacé-Wiens, 2010). The A virus is often sub-typed according to the arrangement of its surface glycoproteins. One of fifteen different hemagglutinin (HA) and one of nine different neuraminidase (NA) are arranged to give a unique identifier to the various viruses. While all the possible combinations of these glycoproteins have been found in avian hosts, only H1N1, H2N2, and H3N2 have been associated with significant epidemics in humans.

Outbreaks of Influenza A occur when the virus' genes mutate, changing its properties and exposing a population to a varied version of the virus. These mutations can occur in two ways, colloquially referred to as *antigenic shift* and *antigenic drift*. *Antigenic shift* occurs when a distinct HA emerges, changing the glycoprotein composition, sometimes resulting in a pandemic. *Antigenic drift* refers to more subtle variations in the virus' structure, but still can cause a partial loss of immunity in a population. *Antigenic drift* is responsible for seasonal epidemics or inter-pandemic influenza. Influenza B can also mutate, but slowly, in a way like *antigenic drift* (Kuszewski, 2000; Lagacé-Wiens, 2010; Lahariya, 2016).

Some influenza endemics begin in avian species. The virus reproduces in the gastrointestinal system of waterfowl and shore birds – which acts as a "reservoir" - where the virus is asymptomatic. It is excreted from the birds into bodies of water where it can infect larger birds and mammals – including humans, horses, seals, whales, and pigs. Endemics can also begin in swine – although human to human transmission of swine flu is extremely rare (Cox, 2000). Transmission between humans occurs primarily through large-droplet aerosols associated with sneezing or coughing, although formites also contribute to the spread of the virus. Once contracted, the virus grows in the trachea and bronchi, where it can spread to infect other individuals (LaForce, 1994).

The reason for the seasonality of the influenza virus remains unknown. Researchers speculate it is associated with crowding during the cold winter months. This belief is corroborated by the increased spread of influenza in schools, dorms, and military compounds. The sterilizing properties of ultraviolet light might also reduce transmission

from formites during warmer months (Lagacé-Wiens, 2010). Seasonal influenza epidemics begin and escalate quickly, typically peaking within two to three weeks and lasting for five to ten weeks. The virus follows a fairly predictable course – first infecting school children before spreading to their parents and guardians before finally reaching the elderly (Lagacé-Wiens, 2010).

This pattern has been known for decades. In a 1982 paper about the morbidity and mortality of influenza in Huston Texas form 1974-1981, W. Paul Glezen documents a reoccurring "age shift" that occurs each influenza season – the age of the individuals seeking medical care due to infection increases as the season progresses. Glezen writes, "during the early stages of the epidcmics, a disproportionate number of cases have been older school-aged children in the 10-to-19-year age range" (Glezen, 1982 p.29). In fact, more than half (53.5%) of the documented infections in the early stages of the epidemic were found in school-aged children. During the late stages of the epidemic, children made up just over a third (35.2%) of all flu-related medical visits. School attendance appears to be one of the driving factors in this trend. The data collected through the 1982 research found that during two of the flu seasons included in the study the virus began to spread most rapidly in early December, but infection transfers slowed later in the winter. Glezen concluded that "that school holidays interrupted and probably dampened the effect of these epidemics on the community" (Glezen, 1982 p.29).

The predictable path of the spread of influenza highlights another important concept in epidemiology – that of *selective vaccinations*. It is more beneficial to vaccinate some individuals than others, and absent a universal vaccination program,

understanding the movement of an infection through a community is paramount to mitigating the economic and medical effects it can have on a population. Epidemiology – the study of the transfer of infectious diseases – helps develop an understanding of who to vaccinate and when to vaccinate them.

1.2. Vaccinations & Epidemiology

Epidemiology studies the spread and control of infectious diseases. It is vitally important to consider epidemiological factors in all research involving contagions, including economic research. Vaccination in particular is one of the most cost-effective interventions that can be implemented among a population (Lahariya, 2016). Vaccinations have been gaining recognition over the past few decades for their importance in controlling disease spread and achieving various public health outcomes. "Vaccine epidemiology," as Chandrakant Lahariya calls it, "could be described as an interface between public health, basic medical sciences, and clinical medicine aimed at maximizing the benefit of existing knowledge in these areas" (Lahariya, 2016, p.2). Economic evaluations in healthcare often omit epidemiological practices and principles which results in inaccurate modeling. Cost-benefit analysis of the influenza vaccination requires an understand of vaccine epidemiology to properly model any scenarios.

A vaccine is typically a lab-made version of the pathogen that can be administered to a host in order to initiate the appropriate immune system response before the pathogen is naturally encountered. The vaccine pathogen or antigen can be inactivated, attenuated, or a lab-created biological substance (Lahariya, 2016). Influenza

vaccinations work by introducing the body to a mutated version of the influenza virus before the host is otherwise introduced to the virus. When successful, the body is able to build the necessary antibodies to protect against natural infection. Despite significant advances in medicine since the creation of the vaccine, the vast majority of it is still produced in chicken eggs and supplied at a rate insufficient to keep up with global demand. Influenza vaccines are typically made to protect against three of the viruses, H1N1, H3N2, and B, although a four-virus variation is in circulation. The success of the vaccine is dependent on the accuracy of the vaccine to the antigens mutated genetic composition. The proximity can vary widely between years, which complicates modeling (Lagacé-Wiens, 2010; Cox, 2000). There is, however, a loose pattern of variation. Cox and Subbarao (2000) write: "each successive antigen variant replaces its predecessor such that the co-circulation of distinct antigenic variants of a given subtype occurs for relatively short periods. During the past decade, new epidemic variations of influenza often are first detected in China before they spread to other locations" (p.411).

Influenza vaccinations reduce infections in a population in three ways. Primarily, they reduce the likelihood of infection in the patient. This additional reduction in the chance of infection is called *vaccine effectiveness* (VE) and is dependent upon the accuracy of the vaccine compared to the seasonal viral strain and varies widely from year-to-year (Ohmit, 2008). Vaccine effectiveness is also dependent on the cohort receiving the vaccination. For example, the same vaccine often has a lower VE in older populations than it does in children and working-aged adults (Kim, 2014). Vaccine effectiveness and vaccine efficacy are sometimes used interchangeably, but they refer to

different concepts. Vaccine effectiveness represents the added resistance to the individual receiving the vaccine; vaccine efficacy is the increased resistance of the population, and sometimes called "program effectiveness" (Lahariya, 2016; Shim, 2012). This research uses VE to represent only vaccine effectiveness – the individual component. The second public health benefit is the "herd" – the reduced likelihood of infection in the unvaccinated population. This effect exists because as vaccination reduces the likelihood of infection in the vaccinated population, it also decreases the total number of infected individuals in a population who are then capable of further infecting the unvaccinated population. Some research has suggested that this indirect effect of vaccinations is greater than the direct effect on the vaccinated population (Pradas-Velasco, 2008). The herd effect and herd immunity are related, but not the same measure. The herd effect is name for the indirect effects of vaccination while herd immunity typically refers to a state in which a group achieves emergent resistance by having a higher vaccination rate than the "herd immunity threshold" (H). The herd immunity threshold is the minimum portion of a population that must be immunized for the entire population to be resistant (Lahariya, 2016). Finally, vaccination has a residual effect that is not realized until future influenza seasons – research shows that previous natural infection and previous vaccination reduce the susceptibility of a population to future infection (Lagacé-Wiens, 2010). Research shows that the herd immunity threshold in the United States is about 80% of the population (Plans-Rubio, 2012).

The speed at which the virus spreads can be evaluated through several different measures, but this research uses exclusively *reproductive rate*. The *natural reproduction*

rate, or R_0, is a measure of secondary infections expected to result from each case of influenza, absent an intervention. R_0 less than 1, for example, indicates an infection is in decline – each person who contracts the virus will pass it on to fewer than one other person, and an epidemic is impossible (Fine, 2011).

$R_0 = 1$ Each case will generate one new case

$R_0 > 1$ An infectious disease, with exponential growth

$R_0 < 1$ A pathogen in decline, each case will produce fewer new cases (Laharya, 2016)

Vaccinations work to reduce the attack rate of a virus by lowering both the infected population and susceptible population. By vaccinating individuals, they are less likely to be at risk of contracting the infection from others, and therefore less likely to pass an infection to others who remain at risk. Reducing the attack rate from R_0 (the rate of spread absent any intervention) to R_1 (the rate of spread with intervention) is dependent on two variables – the success of the vaccination and the adoption of the intervention. The reproductive rate of a pathogen is difficult to measure, and is dependent on various factors such as the means of transmission and the contagious period of the host. The R_0 of influenza is typically estimated to be 1.3, but varies depending on the year (Coburn, 2009).

Some groups are more advantageous to vaccinate than others. Before 2010, for example, the CDC did not recommend vaccinating working-aged adults (ACIP, 2018). As mentioned earlier, selective vaccination of groups can be a highly cost-effective way to reduce incidence among at-risk groups with indirect benefits to the population. For example, the vaccination of healthcare workers can help reduce the circulation of the

influenza virus among healthcare workers. Vaccinating clinicians has been shown to reduce influenza-related hospital admissions by 32-39% and reduced pneumonia and influenza related hospital deaths by 43-65% among patients over 45 years of age (Kim, 2014). Vaccinations of school children are also important and have been shown to slow the spread of disease. In Japan in the 1990s it was shown to reduce morbidity and mortality in the elderly (Fine, 2011). Other studies have corroborated this relationship. Vaccinations administered to elderly populations have a lower VE than those given to the rest of the population, a fact that is troubling given the fact that the elderly have high influenza-associated morbidity rates. In fact, a 20 year-long program intended to protect this high-risk group was successful in reducing morbidity in the United States. As it turns out, the best way to protect the elderly from influenza is to vaccinate the people who would transfer it to them – healthcare workers and family members. This suggests that seniors benefit more from the indirect and herd effects of vaccination than they do from receiving the vaccination themselves (Kim, 2014).

In 2009, Jan Medlock and Alison P. Galvin published *Optimizing Influenza Vaccine Distribution*, in which they developed an age-structured transmission model that tracked 17 age cohorts to evaluate the mixing of peoples and the corresponding spread of disease. The research found that it is most cost effective to vaccinate children and adults aged 30-39. This is because schoolchildren account for a disproportionate amount of disease transmissions and their parents act as "bridges" to the rest of the population. Medlock and Galvin believe their findings are important for determining selective vaccination distribution in a supply-constrained scenario (Medlock, 2009).

Absent the supply constraint, however, public health programs should attempt to vaccinate at least 80% of the entirety of their population and 90% of high-risk individuals according to Healthy People 2020 and Healthy Vermonters 2020. The actual herd immunity threshold varies by year and cannot be predicted. A 2012 paper by Pedro Plans-Rubio calculated the herd immunity threshold for five different flu seasons using R_0, vaccine effectiveness, and vaccine coverage. He concluded that in some years, as little at 30% to 40% coverage is necessary in a population to prevent a seasonal epidemic, but the herd immunity threshold can approach 100% in others. He concluded that the vaccination goals set forth by the United States in 2010 (80% of working-aged adults) were adequate to result in herd immunity in most years, and a substantial herd effect in others (Plans-Rubio, 2012). This research does not use a herd immunity threshold but does consider the herd effect by using a dynamic transition model to capture the indirect benefits associated with vaccination – i.e. the reduction on illness in the unvaccinated population.

1.3. Infectious Disease Transmission Modeling

Infectious disease modeling attempts forecast epidemiological events or test hypotheses and document mathematical patterns of disease as they spread through a population. Dietz and Schenzle (1985) summarize the practice eloquently:

> The focus of concern of infectious disease modeling is the transmission of the disease agents through the population. A detailed model would describe at any time the number of [viruses] in each member of the host population.… The transmission model has to include always two basic components: (a) the course of an infection within one individual once the [viruses] have entered, (b) the mode of spread of [viruses] between individuals (p.169).

Biology typically deals with the first of these components while epidemiology – by necessity – concerns itself with both. In the case of influenza, the course of infection is important to an understanding of how long an individual is contagious, while the mode of spread helps determine the rate of transmission (and therefore the R_0 or attack rate).

These transmission models can be divided into two categories – static and dynamic. Static models "implicitly assume that the probability of disease exposure is unaffected by an intervention against it, and therefore the probability of exposure to the disease does not change over time," and they typically underestimate the effect of vaccination (Lugnér, 2010 p.44; Bauch, 2009; Van Vlaenderene, 2013). Cost-benefit analysis must therefore utilize dynamic models, which incorporate the compounding effects of vaccination over time. (Lugnér, 2010; Pradas-Velasco, 2008).

There have been attempts at approximating dynamic and herd effect modeling in static models, but they are a poor replacement for true dynamic models. In 2019, Chris T. Bauch *et al*. published a paper in which they compared outcomes of a pseudo-dynamic cohort model to those of a dynamic compartmental transmission model. They found that their best efforts approximated the outcomes of an epidemiological model, but only if the reproductive number of the virus was exceedingly high. Any lower than that, or with a small population, and the pseudo-dynamic model fell short of the accuracy of a dynamic model. Bauch *et al*. tested a susceptible-exposed-infected-recovered (SERI) dynamic model, which is very similar to the susceptible-infected-recovered model used in this research. (Bauch, 2009). In 2013, Van Vlaenderen and others published *An Approximation of Herd Effect Due to Vaccinating Children Against Seasonal Influenza –*

a Potential Solution to the Incorporation of Indirect Effects Into Static Models. As with Bauch, Van Vlaenderen's attempts at simplifying the modeling of infectious diseases was only partially successful. The paper compared two previously published linear approximations of disease transmission models (including Bauch's study) but concluded that "a non-dynamic approximation such as those presented here cannot replace a fully dynamic modelling approach and should only be intended for a preliminary assessment of the herd effect" (Van Vladerene, 2013 p.11).

Dynamic transmission modeling is utilized by a minority of economic studies. In fact, between the years of 1976 and 2005, 72% of vaccine cost-benefit analysis did *not* consider the herd effects of immunization programs. Nymark et al. published a systematic review of methods used in economic evaluations of vaccination programs, assessing 172 English-language publications written over 40 years. They concluded that "only 28% of the cost-effectiveness analyses of vaccines in this review included herd immunity effects. 55% used static models, which cannot accurately predict herd immunity," and "there are no recommended methods available for incorporating herd immunity using a static model and the reliability of these results is questionable" (Nymark, 2017, p.6837). Failure to incorporate dynamic modeling into economic models not only misstates the effects of vaccination programs, it limits the discussions and strategies that can be employed by public health professionals by omitting time as a variable (Lugnér, 2010).

A commonly used dynamic transmission model is the susceptible-infected-resistant (SIR) model. This compartmental epidemiological model is used in this research and is described in detail in the methods section. The epidemiological work in this

research is based on the mathematical modeling found in Pradas-Velasco's 2008 paper, *Dynamic Modelling of Infectious Diseases.*

1.4. Cost-Benefit Models

There have been numerous economic appraisals of vaccination programs written over the past 40 years, and each year, the number of new publications increase exponentially (Nymark, 2017). Unfortunately, few of these models incorporate the multidisciplinary approach necessary to truly evaluate the nuances of a vaccination program. Papers written by economists often fail to capture the dynamics of communicable diseases and opt instead to conduct cost-benefit analysis using static models absent epidemiological variables. Conversely, papers written by medical professionals often fail to incorporate the various direct and indirect costs associated with influenza – often omitting variables such as lost productivity. Furthermore, the papers often have too short a time-horizon: even though most of these papers mention the wide variation in influenza illness distribution by year, few of the articles include more than one or two years in their analysis. Each of these papers compare the cost of vaccination to the cost of treatment. Some are cost-benefit analyses; some are cost-effectiveness analyses. Although the model included in this paper draws heavily from each of these publications, a new model is needed to compare the total societal cost of influenza before and after an intervention. The model must include a larger time horizon, all societal costs, and a dynamic disease transmission component.

This summary of cost-analysis literature was conducted by evaluating two published systematic reviews: Ting et al. and Nymark et al., both published in 2017. Ting et al. provided a review of cost-effectiveness research while Nymark et al. reviewed methods used to calculate herd immunity. Only papers that used cost-effectiveness analysis, cost-benefit analysis, or dynamic infectious disease modeling were included in this literature review. Additional sources were included whenever they were heavily cited in the papers found through the two systematic reviews.

In March 2017, Ting, Sander & Ungar published *Systematic review of the cost-effectiveness of influenza immunization*. The authors used a systematic literature search to identify 31 studies published between 1996 and 2014. A database search produced 4,221 individual economic publications. Title and abstract screening reduced this number to 41 studies that evaluated entire populations or sub-groups for any immunization vaccination formulation. Applying quality appraisal further reduced this number to just 31 publications. Twenty-one of these studies were conducted on healthy, working-aged adults. These publications, in addition to literature on Vermont's population and health costs and epidemiological SIR models, and other cost-benefit research are the foundation of this study.

In general, the studies sought two different results. Studies that sought to calculate the cost of a quality adjusted life year (QALY) are of less value to this research (Maciosek *et al*., 2006; Sander *et al*., 2010). While they provide useful information on various cohorts, they do not utilize the framework which will be implemented here. QALYs are a useful tool, but the goal of this paper is to compare the societal costs of two

methods of vaccine distribution, and not calculate the cost of added years of life. The other studies calculated "breakeven" points: dollar values which the cost of administering the vaccination would need to be below to economically justify a universal vaccination.

This research draws more from the latter of these study types to construct the cost-benefit model. Similar to the breakeven models, both indirect and direct costs will be included in the analysis. However, a key difference is how the costs will be compared. In the breakeven models, the average societal cost of vaccination is compared against the societal cost of illness. In the case of this research, the cost of vaccination ($VCost_0$) and illness ($TCost_0$) will be summed *together* and compared to the cost of vaccination ($VCost_1$) and illness ($TCost_1$) after an intervention, to determine the cost effectiveness of the intervention.

The first placebo-controlled cost-effectiveness study of influenza vaccines was published in 1995 by Kristen L. Nichol *et al*., but it was not included in the Ting review because it fell outside the timeframe. Although the associated costs and benefits have evolved over the past 20-plus years since its publication, *Nichol et al.* create a framework which has become the basis for many of the studies included in this literature review. This research studied 849 subjects between the ages of 18 and 64. Half of the subjects were given a placebo; half were given the flu vaccine. The research used US dollars to calculate costs/savings and included the cost of vaccination, medical care for side effects, and medical care avoided due to vaccination for direct costs. Indirect costs included work time lost due to vaccination, illness, and side effects. This research calculated a cost savings of $46.85 in 1995 USD per person vaccinated and concluded that "vaccination

against influenza has substantial health-related and economic benefits for healthy, working adults" (Nichol, 1995, p.891).

The first breakeven study was published in 2000 by Carolyn Buxton Bridges *et al*. The authors note that while the benefits of vaccination for individuals over 64 years old is well documented, there is a lack of studies evaluating 18-to-64-year-olds. The researchers conducted a randomized, double-blind trial with placebo controls over the course of two flu seasons. The study calculated the cost of administering a vaccination as $24.70 per person. This included the $10 vaccine (supplies + nurse's time), and 30 minutes of lost work time for the patient. The study then calculated the average influenza-like illness (ILI) cost for each group and added it to the cost of the vaccination.

The results varied dramatically between the two years. This is because the vaccination circulated in the first year of the study (1997-1998) was largely ineffective. The ILI costs alone in the influenza group were almost twice as high as in the placebo group. The total cost of year one was $124.21 per vaccinated person and $58.62 per unvaccinated person.

In the second year of the study, the vaccination was more effective. Only 14% of the vaccinated group became ill, compared to 21.5% of the placebo group. This resulted in ILI costs of $26.73 in the vaccinated group and $40.26 in the control group. Still, after adding the cost of vaccination, the total cost of the vaccinated group exceeded the placebo group at $51.43 (Bridges, 2000). This study suggests that vaccinating healthy, working-aged adults would not be cost-effective. However, the population of this study was rather small – it looked only at employees of Ford Motor Co. in Dearborn, Michigan.

It also calculated the cost of vaccination for individuals with hourly salaries of $30, well above Vermont's average wage. Certain assumptions would need to be changed to make these findings applicable to Vermont. More importantly, this study did not consider the indirect effect of vaccination – herd immunity. Throughout the literature, and within this study itself, it is evident that the marginal cost of vaccinating an individual is less than the benefits associated of lowering their chance of infection.

In 2001 Kristin L. Nichol published *Cost-Benefit Analysis of a Strategy to Vaccinate Healthy Working Adults Against Influenza*. It is the second of three papers written by Nichol that are included in this literature review, and a foundational piece of research for the cost-benefit modeling for Vermont's population. Here, Nichol takes the societal perspective, and incorporates all costs both direct and indirect. Nichol's basic cost model is as follows:

Net Costs (Savings) = Cost of Vaccination – Costs Averted Due to Vaccination

The variables used include illness rate, the percent of cases medically attended, work absenteeism, hospitalization rates, dosage prices, Medicare reimbursement rates, health care provider visits, medications, and the hourly wage of patients. Nichol also considered the cost of the side-effects associated with the vaccination: although there was a slight increase in reported side-effects from a vaccinated cohort (when compared to a placebo group), Nichol writes that "the most likely estimate for work absenteeism and health care provider visits due to side effects from vaccination [itself] is close to 0" (Nichol, 2001 p.751). Neither Nichol's 2001 paper nor this research include a willingness-to-pay variable for avoiding side effects.

Nichol calculated the potential for societal savings using Monte Carlo simulation, and concluded that the "mean cost per person vaccinated… resulted in net savings of $13.66 for each person vaccinated" (p.753). The results varied from savings of $174.32 per person to a cost of $21.27 per person. Overall, however, the model showed that vaccination resulted in net savings 95% of the time (Nichol, 2001). Nichol's research was most sensitive to the illness rate and the lost productivity of the population. The research did not use a dynamic epidemiological model to capture the herd effect of increased vaccination rates – it only evaluated the cost of vaccinating individuals against the associated healthcare savings. If Nichol truly wanted to take a societal perspective, her model should have included more epidemiological factors.

A year later, Patrick Lee *et al*. published *Economic Analysis of Influenza Caccination and Antiviral Treatment for Healthy Working Adults* (2002). This piece of research reviewed previously published data to calculate the net benefit of influenza vaccination from a societal perspective. Healthy, working adults aged 18 to 50 were included in the study. The net benefit of the various treatments examined was simply calculated as:

Net benefit (cost) = benefits of vaccination and treatment – cost of vaccination and treatment

The research used a static decision-tree model to evaluate the costs of various vaccination and treatment paths and took a societal perspective, accounting for direct and indirect costs and benefits. Lee *et al*. assigned various probabilities and costs to each branch of the decision tree and altered those probabilities to assess the cost-effectiveness of various scenarios. The economic benefits are only visible when epidemiological

factors are considered (Valenderene, 2013). Instead, Lee *et al*. used a linear model that did not account for the increasing marginal benefits of additional vaccination – the herd effect. Lee *et al*. also used an unusually high value for lost productivity – 2.8 days. This number may have offset the reduced savings associated with static models. The authors note that they assumed "return to normal activity" as a return to work.

Lee *et al*. concluded that vaccination provided a net benefit to society both when paired with antiviral treatment and alone. Vaccination alone provided a net benefit of $29.50 per person vaccinated. The researchers compared their results to those of Nichol *et al*. and contrasted their work to that of Bridges for two reasons. First, Bridges *et al*. did not consider the costs/benefits of side effects from influenza medications. Lee *et al*. evaluated these using a willingness-to-pay survey and included it in their calculation. Second and more important, Bridges *et al*. calculated the lost productivity at 0.5 workdays per episode. The Lee *et al*. research states that if they had used 0.5 days per episode instead of 2.8 (a number previously published in two studies) the resulting analysis would not have been cost-effective. (Keech, 1998; Schoenbaum, 1987).

The most contemporary study addressed in the Ting, Sander & Ungar systematic review was written by Nichol, Mallon, and Mendelma. *Cost Benefit of Influenza Vaccination in Healthy, Working Adults: An Economic Analysis Based on the Results of a Clinical Trial of Trivalent Live Attenuated Influenza Virus Vaccine* was published in 2003, and is somewhat divergent from the prior studies in both subject and methods. First, this piece of research focuses only on vaccination by live attenuated influenza virus vaccine (LAIV) – a nasal spray. Second, although the study conducted a placebo-

controlled blind study to calculate decreased health care utilization and workplace absenteeism, the study relies more heavily on alternative sources to produce some of its estimates. Third, this study included a calculation of "reduced effectiveness" to account for the reduced productivity of employees who work through their illness. The study also calculated a "breakeven cost" rather than a savings/loss per person.

A 2005 cost-effectiveness study conducted by Michael B. Rothberg and David N. Rose concluded that the vaccination of health working-aged adults was "reasonable economically, and in certain circumstances is cost saving" (Rotherberg, 2005 p.68). The analysis used ten years of surveillance data from the World Health Organization and measured outcomes in illness days, costs, and QALYs. The research tested various strategies including increased vaccination, treatment with amantadine therapy, and the status quo over the course of the ten years. The researchers found that the most economical public health strategy varied from year to year. This research did not evaluate the herd effect of vaccination in any way.

Unfortunately, although much can be learned from each of these studies, none of them are robust enough to fully capture the costs and associated benefits of a vaccination program. Few of these studies were conducted over a long enough period to properly account for the annual variations in proximity between vaccine and virus antigens. It is possible for a vaccine to be highly cost-effective one year and ineffective the next. The studies that were often cited used liberal figures for key variables such as reduction in workforce productivity. By far the most persistent noteworthy omission from these studies is consideration for the epidemiological factors of vaccination programs. This

research intends to address these shortcomings in order to create a model that is societal in measure, dynamic in nature, and more longitudinal in scale.

1.5. Regional Universal Influenza Vaccination Programs

Two communities in our region have already implemented universal influenza vaccination programs: Ontario and Rhode Island. Rhode Island runs its program through a vaccine purchasing program like the VVPP mechanism referenced in this research. Unfortunately, little data has been made available.

Rhode Island includes all vaccinations recommended by ACIP in its adult vaccination program – including influenza. The state administered over 450,000 doses of the flu vaccine during the 2015-2016 season. As of 2016, vaccination rate growth has been modest, increasing from 37.6% of 18-to-49-year-olds during the 2011-2012 season to 45.4% during the 2015-2016 season. By 2015 the state saw an increase in vaccination rates from 67% to 88.5% among healthcare workers, and claims that the inclusion of influenza in their vaccine program eliminated a cost barrier and increased access in such a way that racial and ethical disparities were reduced. Unfortunately, no further analysis has been conducted by Rhode Island (RI, 2015).

Ontario, on the other hand, has had several journal articles published on the topic of universal influenza vaccinations. Ontario introduced its "universal influenza immunization program" (UIIP) in 2010 for all residents aged 6 months and older. The program has been associated with higher vaccination rates in children and adults and a

reduction in influenza associated mortality and health care usage. A 2010 paper by Beate Sander *et al*. tested the cost-effectiveness of the program with multivariate regression supported by sensitivity analysis. The research created a historical baseline for influenza costs and medical visits and studied the effect of Ontario's UUIP using nearby non-universal providences as a control group. The primary goal of this research was to establish a cost per quality adjusted life year (QALY) gained through the UIIP. Although QALYs are not of particular interest to this study, many of their other findings are.

Sander *et al*. concluded that although the UIIP was twice as expensive as a targeted-population program, influenza cases were reduced by 62% and influenza-associated mortality fell 28%. The reduction in hospital visits and end-of-life care are largely responsible for an overall reduction in influenza treatment service costs by 52%. Unfortunately, the researchers indicated that the study design does not effectively prove causality between the findings and the UIIP. It should be noted that this research did not conclude that the program was cost-effective.

According to the research, the UIIP cost $40 million Canadian dollars (CAD) to run as opposed to the $20 million CAD cost of a targeted program. The $20 million CAD increase was partially offset by a $7.8 million CAD decrease in healthcare costs – resulting in a $12.2 million CAD cost of running the UIIP program – a cost the research still called "economically attractive" (Sander, 2010 p.6). This analysis *did not* account for indirect costs of influenza. There was no calculation of lost productivity – only direct medical costs were included. If an indirect variable had been included, the results might have shown an increase in QALYs and a reduction in economic cost.

1.6. Vaccination Trends and Goals

Healthy Vermonters 2020 is Vermont's health assessment plan. This most recent iteration of Healthy Vermonters represents the third decade of the program, in which the Vermont Department of Health has set various health assessment goals that will ideally be met by 2020. Any of the indicators included in *Healthy Vermonters 2020* is taken from the national initiative, *Healthy People 2020. Healthy People 2020* was created with the objective of leveraging technological advancements and federal-state partnerships to increase the life expectancy of Americans. The program identifies vaccines as being "among the most cost-effective clinical preventative services" that can be provided to a community (ODPHP, 2018). One of the selected objectives of *Healthy People 2020* is to "increase the percentage of noninstitutionalized adults aged 18 to 64 years who are vaccinated annually against seasonal influenza." The goal set forth by the program is to have 80% of the target population immunized by 2020.

Coinciding with *Health People 2020* is Act 191 – a section of the Vermont statute written in 2006 that created the Vermont Vaccine Purchasing Program (VVPP). The act states that the Vermont Department of Health (VDH) will administer an immunization program ensuring "universal access to vaccines for all Vermonters at no charge to the individual and reducing the cost at which the State may purchase vaccines" (18 V.S.A. §1130, (b)(1)). The law continues to describe how the program will be organized and the data collected by the Vermont Department of Health. Vaccines included in the VVPP are to be purchased by the State from the CDC at the lowest possible cost. VDH is required

to provide for the administration of the program, and insurers must remit the cost of both dosage and administration in the form of a per-member-per-month assessment calculated by an external vendor (18 V.S.A. §1130). This law is specific to Vermont, but similar statutes exist across the country. The VVPP is the most likely means of executing a universal vaccination program and is the basis of the usage of CDC contract dosage prices used in the methods section of this research. The VVPP, however, can only provide vaccines free of charge to primary care providers. Other administers of the flu vaccine such as pharmacies, employers, schools, and retail stores must purchase the vaccine themselves. Nevertheless, the VVPP is a potentially highly useful mechanism for helping the state approach the influenza immunization goals laid out in both *Healthy Vermonters 2020* and *Healthy People* 2020.

Vermonters have their influenza vaccines administered in a variety of settings. Traditional care settings such as hospitals and clinics have yielded considerable volume to pharmacies, retail stores, and workplaces. Vermont's Behavioral Risk Factor Surveillance System (BRFSS) includes influenza vaccination questions in its annual survey. Each year, the survey asks respondents if they have received an influenza vaccination in the last twelve months. Unfortunately, the survey only asked respondents to indicate the location they received the vaccination in three years: 2011, 2012, and 2015. About 4,000 individuals responded to this question each year; a little under half of them indicated receiving a vaccination at all.

Table 1: Vermont Vaccination Locations by Year

Vaccination Location	2011	2012	2015	Weighted Average
Doctor's Office	17.27%	15.39%	15.22%	16.03%
Work	10.66%	9.53%	11.12%	10.45%
Store	3.09%	4.03%	7.28%	4.72%
Hospital	3.74%	3.80%	2.34%	3.31%
Clinic	3.46%	3.01%	2.12%	2.89%
Other	1.04%	1.17%	1.15%	1.11%
School	1.02%	0.31%	0.72%	0.70%
VDH	0.41%	0.20%	0.40%	0.34%
Community Center	0.28%	0.13%	0.12%	0.18%
ER	0.02%	0.00%	0.07%	0.03%
Unvaccinated	59.01%	62.44%	59.44%	60.22%

Note. 4,626 responded to this question in 2011; 3,924 in 2012; and 4,009 in 2015.

Table 1 includes data taken directly from BRFFS data from the years 2011-2016. It includes only years in which the point-of-service question was asked. Data is for individuals who indicated they were between 18 and 64 years-old. The survey responses were evaluated in SPSS using simple cross-tabulation. The data suggests a migration of flu shot administration away from doctor's offices and into stores. Unfortunately, the definition of "store" is left up to the respondent, but it likely includes stores with pharmacies, such as convenience stores and supermarkets. Over all the years included in the data, women (50.3%, n=21,223) were more likely to be vaccinated than men (44.3%, n=15,732) and respondents with an annual household income over $75,000 (51.6%, n=18,111) were more likely to be vaccinated than respondents with an annual household income under $75,000 (45.2%, n=7,555). More information on the BRFSS survey itself is included in the next section.

1.7. Data Sources

This research relies heavily on data from the State of Vermont and the Centers for Disease Control and Prevention. Medical claims data comes from the Vermont Healthcare Claims Uniform Reporting and Evaluation System (VHCURES). The authority to collect and maintain medical claims information for state residents was initially given to the Department of Financial Regulation. In 2013 that authority was transferred to the Green Mountain Care Board (GMCB). The law states, "The Board shall establish and maintain a unified health care database…" which includes patient and provider identifiers, a uniform coding system, and information on all health care costs, utilization, and enrollment information (18 V.S.A. §9410, (a)(1)). All health insurers, "third-party administrators (TPAs), pharmacy benefit managers (PBMs), hospitals and health systems, administrators of self-insured or publicly insured health benefits plans, and any other similar entity with claims data, eligibility data, providers files and other information relating to health care provided to Vermont residents" are required to provide electronic claims data to the GMCB, which is responsible for collecting, storing, and distributing data and statistical reports to interested and approved parties (GMCB, 2018). Individual Vermont residents are permitted to opt-out of data sharing, and all external reporting of the data must align with HIPAA regulations. The act also states that the GMCB must collaborate with the Vermont Agency of Human Services, which is how the data was made available for this research. It is a complete, comprehensive, and near-universal data set with extraordinary potential for health care research.

Data from Vermont's Behavioral Risk Factor Surveillance System (BRFSS) is collected to better understand personal health behaviors of Vermonters. Although it is not used in the economic or epidemiological modeling, BRFSS data helps provide context to the issues addressed in this research. The surveillance system is a telephone survey of randomly selected Vermont adults. The survey interviews between 6,000 and 7,000 residents each year, reaching out to residents through both land and cellphone lines – there is potential for a self-selection bias. Each of the 50 states and the District of Columbia have a BRFSS. Questions are typically about issues that are of interest to public health: chronic disease prevalence, access, risk behaviors, and demographical information is collected. Immunization information is collected as a means of assessing the preventive behaviors of Vermonters; however, the questions asked in each survey are not always consistent. The BRFSS helps inform many of the metrics for the *Healthy Vermonters 2020* and *Healthy People 2020* indicators, and plays a role in supporting the immunization registry, which provided key variables for epidemiological modeling.

Much of data in this model comes from the Centers for Disease Control and Prevention, which is itself compiled from various surveys and studies conducted across the country. FluVaxView data (used to generate vaccination rates in the epidemiological modeling) comes from the National Immunization Survey–Flu, the National Health Interview Survey, the BRFSS, and the Pregnancy Risk Assessment Monitoring System. State and national surveys report their data to the CDC, which compiles, organizes, and analyzes it. FluVaxView data is presented in a web-based dashboard where it can be used by the public. The categorization of information, however, is not the same from year to

year. Vermonters 18 to 64 years old were not grouped together for each year of FluVaxView's existence. The years the data was available (2010 onward) provided a boundary for this study, as metrics for a larger time frame were not easily available. It should be noted here that at the time this research was conducted, VHCURES claims data was only available from 2010 – 2015 – thus limiting this project to five years.

CDC data was used for two other key variables in the cost-benefit model: estimating the vaccine effectiveness in a given flu season, and estimating the medically attended influenza rate. The vaccine effectiveness is gauged through CDC-conducted studies that attempt to measure the additional benefit of a seasonal flu vaccine. The CDC works with various universities and hospitals to conduct observational studies using "medically attended laboratory-confirmed flu" as the outcome; the group of researchers is called the "U.S. Flu Vaccine Effectiveness (VE) Network" (CDC, 2018). Five study sites measure VE using a highly effective rRT-PCR lab test to test for the influenza virus. Each of the studies compares the odds of being vaccinated prior to the medical visit for all confirmed cases of influenza. The results are then adjusted for various location and biological demographics.

CDC data estimating averted illnesses were interpolated to estimate the percent of influenza illnesses that were medically attended for each of the study years. Annually, the CDC uses vaccine effectiveness, vaccine coverage, and influenza hospitalization rates to estimate averted illness, medical visits, and deaths by age cohort. This research compares the sum of the averted medical visits and deaths to the total estimated averted illness to arrive at an estimated percent of medically attended influenza by year. Data is for all

adults age 18-64 across the entire U.S. and is assumed to be representative of Vermont's populations. The CDC warns that since the data is based on telephone survey responses, recall bias, self-selection bias, and low response rates are limitations (CDC, 2018).

CHAPTER 2: METHODS

This study uses cost-benefit analysis centered around a compartmental dynamic transmission model. It takes a historical perspective, beginning with the five historic flu seasons between 2011 and 2015, and asks the question, "What savings or additional costs would have been incurred over the five flue seasons between 2010 and 2015 if the vaccination was made free and available to all Vermonters?"

The cost analysis compares the per-capita annual economic impact of influenza in Vermont before and after two interventions: the inclusion of influenza in the Vermont Vaccine Purchasing Program and a 10 percent increase in vaccination rates.

Because this research takes the historical perspective, many of the cost variables are known or can be derived from claims data. In some cases, prior studies were utilized. The epidemiological variables, however, were not readily available. A *susceptible-infected-resistant* (or SIR) model was used to estimate rates of illness during the study period, as well as to incorporate the effects of herd immunity into the cost-analysis.

2.1. Susceptible-Infected-Resistant (SIR) Modeling

There are two different categories of models that can be used to evaluate disease transmissions – static and dynamic. Static models are simpler (and often based around linear equations) but they fail to capture the herd effect that is often a key component in infectious disease modeling. Although pseudodynamic approaches have attempted to capture herd effects without introducing derivatives, a true dynamic model is best suited

to capture the economic factors associated with influenza vaccination programs (Van Vlaenderen, 2013).

The SIR model, depicted in Figure 1, is a rudimentary dynamic transmission model often used in epidemiology. This compartmental model classifies the population into three categories: susceptible, infected, and resistant. Because influenza is a communicable disease, static economic models often fall short of capturing the epidemiological components. An individual's probability of infection at any point in time is a factor of the number of infected individuals in the population, and both variables change over an influenza season (Pitman, 2012).

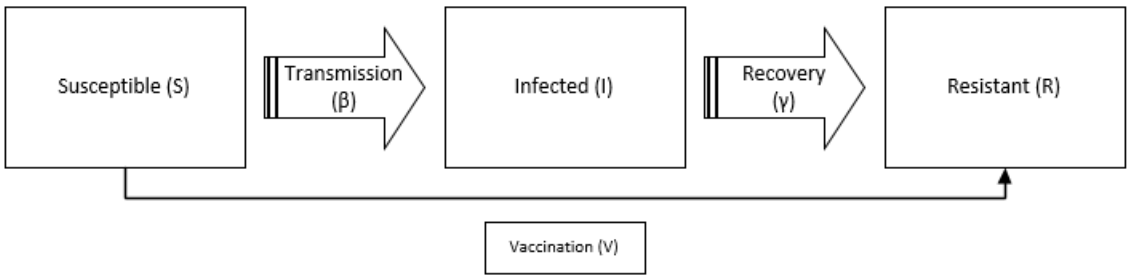

Figure 1: SIR model diagram

The model works by moving individuals between three categories. *Susceptible* individuals are individuals who are not sick and not resistant, and therefore at risk of infection. *Infected* individuals are people who have the influenza virus and are contagious. *Resistant* individuals (sometimes called "recovered") are individuals who are not at risk of infection. This study uses "resistant" because it is possible to become

resistant through vaccination in addition to recovering from illness. The relationship is best represented in a series of differential equations:

$$S'(t) = \frac{-\beta * I(t) * S(t)}{n}$$

$$I'(t) = \frac{\beta * I(t) * S(t) - (\gamma * I(t))}{n}$$

$$R'(t) = \frac{\gamma * I(t)}{n}$$

Here, β is the coefficient of transmission, the rate at which infected individuals transmit the disease to susceptible individuals; γ is the coefficient of natural retirement, the length of time (modeled here in weeks) in which an individual is most contagious; n is the population; and *S, I,* and *R* are the percent of the population that are susceptible, infected, and resistant at any point in time *t.* Here, *t* is a representation of weeks. Both β and γ are derived from literature. γ is taken fromfrom Pradas-Velasco (2008), and β is calculated from an R0 of 1.3 (Coburn, 2009) using the following equation from Pradas-Velasco:

$$\beta = R_0 * \gamma$$

R_0 is the reproductive rate of the virus represented as the average amount of susceptible infected for every sick individual – this figure can be found in the literature.

As mentioned above, vaccination increases the pool of resistant individuals without having them first become infected. It complicates the model slightly:

$$S'(t) = \frac{-\beta * I(t) * S(t) - v(t)}{n}$$

$$I'(t) = \frac{\beta * I(t) * S(t) - (\gamma * I(t))}{n}$$

$$R'(t) = \frac{\gamma * I(t) + v(t)}{n}$$

where individuals are moved directly from the susceptible category to the resistant category at a rate of *v*, which is calculated as the "effective coverage" of a vaccination, or the percentage of the population vaccinated multiplied by the vaccine effectiveness. As either of those factors increases, so does *v*, and more individuals are moved from the susceptible group to the resistant group, leaving a reduced portion of the population to become infected and therefore infect others.

It should be noted that the above equation provides a theoretical framework which has been applied to this project using discrete time modeling, with one-week intervals. The actual equations used in the discrete time SIR model are as follows.

$$S(t) = -\beta * I(t-1) * S(t-1) - v(t-1)$$

$$I(t) = \beta * I(t-1) * S(t-1) - (\gamma * I(t-1))$$

$$R(t) = \gamma * I(t-1) + v(t-1)$$

Table 2: SIR model variables

Year	n	β	γ	*Ro*	*V*	*VE*	*v*	*Population Infected Annually*
2011	1.000	0.557	0.429	1.3	0.389	*0.60*	0.233	0.065
2012	1.000	0.557	0.429	1.3	0.365	0.47	0.172	0.096
2013	1.000	0.557	0.429	1.3	0.411	0.49	0.201	0.084
2014	1.000	0.557	0.429	1.3	0.421	0.52	0.219	0.074
2015	1.000	0.557	0.429	1.3	0.412	0.19	0.078	0.190

Note. The portion of the population identified as susceptible, infected, or resistant at any point in time is represented as a percentage.

Table 2 shows the SIR variables used for each year of the study. In the case of this model, γ, and R_0 were taken from literature (Pradas-Velasco, 2008 and Coburn, 2009 respectively) and β was calculated using the equation provided above. Determining the R_0 for seasonal influenza can be very difficult: there is no good record of how many individuals in a year contract the virus, and disease resistance in individuals can carry forward from previous years – this research used an R_0 of 1.3 for each of the historic years, which was identified as the mean for seasonal strains of influenza (Coburn, 2009; Biggerstaff, 2014). The coefficient of natural retirement, γ, can also be found in the literature: Chowell *et al.* in 2008 determined it to be 4.1 days; n the same year Pradas-Velasco *et al.* used 3.5 days, deviating from previous research (which indicated a natural retirement coefficient of 3 days) to have their model better fit empirical data. This model uses a γ of 3 days (expressed here as .429 weeks) to fit the model to the generally accepted prevalence of influenza – between 5 and 20 percent, depending on the year (Biggerstaff, 2014). A γ of .429 results in a β of .557 once it is multiplied by R_0.

After β, γ, and R_0 were used to form the basis of the SRI model, weekly effective vaccination coverage (EC) was calculated using historic vaccination (V) and vaccine effectiveness (VE) rates. Historic Vermont vaccination rates were taken directly from the CDC immunization registry data for ages 18 to 64. Medical claims data was queried to find the distribution of vaccines in each of the study years. The claims data was used to distribute the historic vaccination rates across the influenza seasons – resulting in an estimated percent of the population vaccinated each week. This number was multiplied by seasonal VE to produce EC by week. The VE is then applied to the SIR model. The

susceptible population in a given week was multiplied by the weekly effective coverage to determine how many individuals are moved directly to the resistant population, thereby skipping the infected category, and reducing both the individuals transmitting the disease as well as the individuals to which the disease can be transmitted. Figure 2 shows weekly vaccination estimates, derived from medical claims data and CDC reported vaccination rates for adults 18-64.

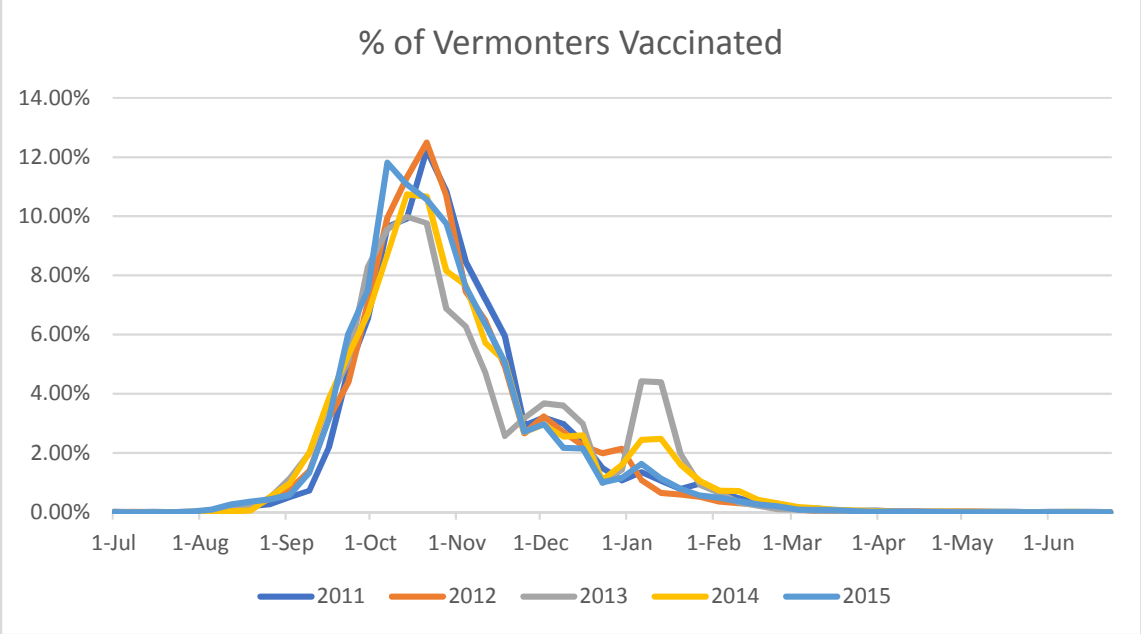

Figure 2: Vermont influenza vaccination trends by year

Discussions with Vermont's state-run immunization program suggest that the first cases of influenza typically begin the first week of December (the 23rd week of the identified flu season), which this research reflects. The percent of the population estimated to be initially infected was set at 0.175% for each year of the study. This figure fits the model to the expected prevalence of influenza in a population, derived from the literature.

The results of the SIR model were then incorporated into the cost analysis model to understand the frequency with which Vermonters became infected with influenza and received medical treatment. The model also allows for the incorporation of a potentially higher adoption rate due to increased access to the vaccination. By adjusting the V in the SIR model, we can accommodate the benefits of the decreased risk of infection of *unvaccinated* individuals that is isolated with the herd effect.

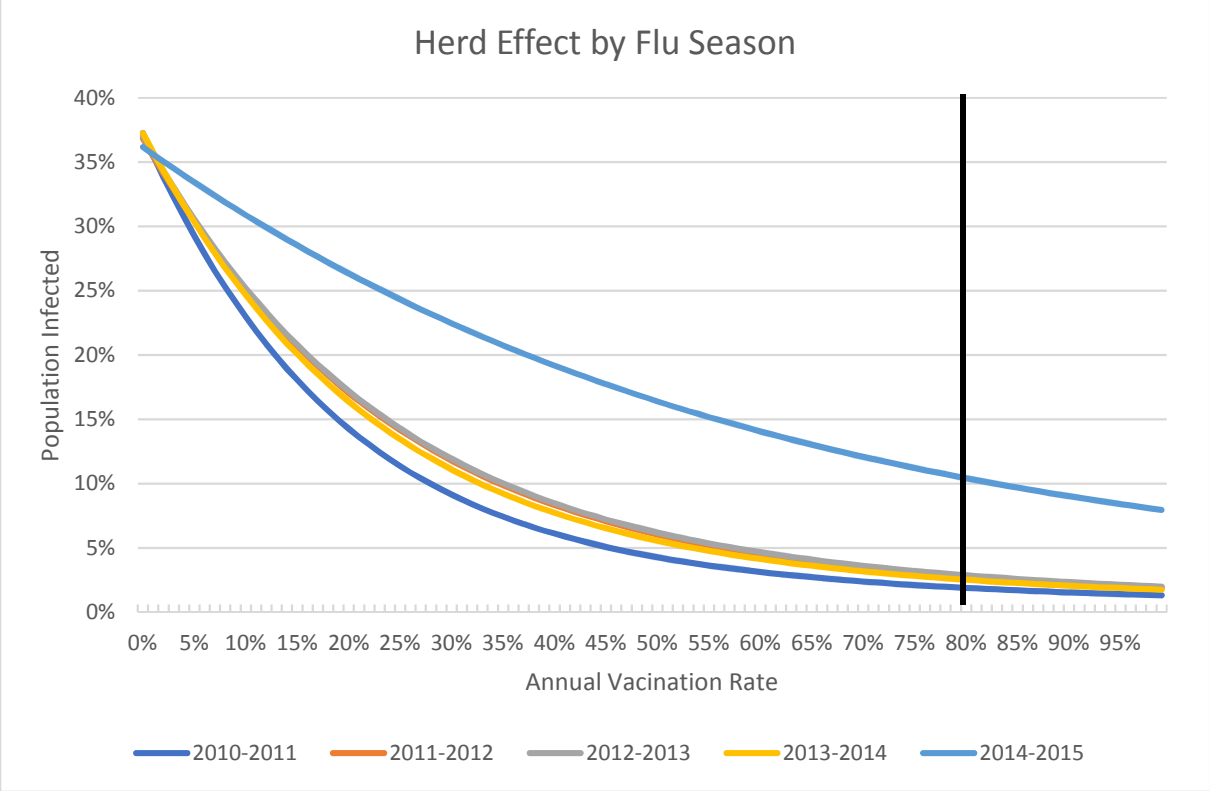

Figure 3: Herd Effect by Flu Season

Figure 3 shows the relationship between vaccination rate and infection rate for each of the five study years. The Healthy Vermonters and Healthy People goal of an 80% vaccination rate is depicted by a black vertical line. This graph brings to light several complications of herd immunity. First, it is important to note that there are still diminishing returns on the increase in vaccination rate. Each new dosage results a smaller

reduction in the annual infected population than the last. The dynamic nature of herd immunity, however, means that these returns diminish slower than if only the direct effects of vaccination are considered.

Second, even with 100% vaccination coverage there are still sick individuals in this model. This is because the graph above assumes same distribution of vaccinations across the flu season as the data indicated. If all of these individuals were vaccinated in the late fall, before the beginning of the flu season, the infection rate at 100% vaccination coverage would be much closer to zero. It's also important to consider the vaccination effectiveness each year. The 2014-2015 season, for example, had a vaccination effectiveness of only 19% - meaning that even with a fully vaccinated population, the effective coverage would still only be 19%. This graph does take into account the initial infection percentage by multiplying the aforementioned 0.175% by the change in size of the resistant population at the onset of the epidemic.

Although a herd immunity threshold is an important concept to study and a good goal for a public health system to try to achieve – it is largely dependent on factors outside the control care providers: the vaccine effectiveness and the timeframe in which the vaccines are administered.

2.2. Cost Analysis – Historic Variables

The cost analysis model compares the societal direct and indirect costs of influenza vaccination and treatment before and after an intervention. All costs are

represented per Vermonter aged 18 to 64, and the same methods are repeated for each of the five study years. All costs are reported in 2017 U.S. dollars. The Bureau of Labor Statistics' CPI inflation calculator was used to bring all costs contemporary. All medical costs are represented as "total reimbursed." This figure ignores the amount charged by the providers, and instead sums all payments made by insurers and individuals (in the form of payments, copayments, prepayments, coinsurance, and deductibles).

At its most fundamental level, the model is:

$$\big((VRate_0 * VCost_0) + (TRate_0 * TCost_0)\big) - \big((VRate_1 * VCost_1) + (TRate_1 * TCost_1)\big) = Savings\ Per\ Capita$$

where $VRate_0$ is the historic vaccination rate; $VCost_0$ is the historic vaccination cost; $TRate_0$ is the historic treatment rate; $TCost_0$ is the historic treatment cost; $VRate_1$ is the altered vaccination rate; $VCost_1$ is the altered vaccination cost; $TRate_1$ is the altered treatment rate; and $TCost_1$ is the altered treatment cost. Table 3 gives an overview of each model variable and its components. In this model, "treatment cost" refers to all direct and indirect costs affiliated with influenza illness, including work absenteeism.

Table 3: List of Cost Model Variables

Variable	Component	Calculation	Source

VRate	Vaccination Rate	Taken directly from the Vermont vaccination registry	US CDC, 2017
VCost	Dosage	0: an average of all dosage lines from Vermont claims data 1: CDC pricing data and VT claims data weighted by BRFSS survey data	VCHURES Claims Data; CDC Vaccination Pricing; BRFSS Survey
VCost	Clinician	Taken from Claims Data CPT Code 90471 "Immunization administration for Vaccines/Toxoids"	VHCURES Claims Data for each individual year and inflated to 2017 USD
VCost	Productivity	Lost productivity of patient due to vaccination. ½ hour multiplied by average VT wage each year.	Buxton Bridges, 2000; Vermont Department of Labor - inflated
VCost	Program Administration	Only in intervention – 1: the added cost of administering the Vaccination program	KidsVax Contract
TRate	Treatment Rate	SIR Dynamic Transmission Model	Paradas-Velasco, 2008
TCost	Medical Care	Claims data for commercially insured 18-64-year-olds. Multiplied by medically attended % of infected	VHCURES Claims Data, US CDC, 2017
TCost	Medicine	Over the counter medicines, adjusted to 2017 USD	Molinari, 2007
TCost	Productivity	Two days of missed work multiplied by average Vermont wage, adjusted to 2017 USD	Bridges, 2000 Vermont Department of Labor
TCost	Pharmaceuticals	Weighted average cost per patient, adjusted to 2017 USD	Bridges, 2000

Historical vaccination costs were queried from the Vermont Health Care Uniform Reporting and Evaluation System (VHCURES) medical claims data. Service dates were grouped into flu seasons, each beginning on the first of July and ending on June 30 the following year. The claims data were then reduced to show only payments made on claims lines with an influenza vaccination, identified by the following Current Procedural Terminology (CPT) codes: 90630, 90674, 90682, 90685, 90686, 90687, 90688, 90749, 90756, 90656, 90658, and 90673. Each of these codes represents a different vaccine administered. The claims were further reduced to include only claims paid by commercial insurers, and exclude patients over the age of 65 or under the age of 18, individuals residing out of state, and claims that were denied by the insurer.

The average cost (across all payers) was calculated by vaccine type (determined by CPT code) and weighted by the frequency with which the vaccines were administered to estimate the average total reimbursed costs of all vaccines across all payers. Of the 12 CPT codes originally queried, only four were used throughout the course of this study. These four vaccination types accounted for 99.98% of all influenza vaccines administered, and VHCURES data and the Green Mountain Care Board disallow the reporting on such small samples to protect patient confidentiality. The weighted cost by flu season is used in the economic model.

Table 4: Vermont Vaccine Costs and Weights by Flu Season

		2010-2011		2011-2012		2012-2013		2013-2014		2014-2015	
Vaccine	**CPT**	**Cost**	**%**	**Cost**	**%**	**Cost**	**%**	**Cost**	**%**	**Cost**	**%**
Afluria (IIV3) multi-dose vial	90658	$ 17.15	0.742	$16.55	0.729	$17.66	0.655	$17.30	0.563	$ 15.17	0.393
Fluzone (IIV4) single-dose vial	90686	$ -	0.000	$ -	0.000	$ -	0.000	$20.50	0.011	$ 29.62	0.291
Afluria (IIV3) single-dose syringe	90656	$ 24.82	0.258	$20.89	0.271	$20.07	0.345	$18.69	0.414	$ 18.12	0.250
Afluria (IIV4) multi-dose vial	90688	$ -	0.000	$ -	0.000	$ -	0.000	$16.73	0.011	$ 18.56	0.066
Weighted Average		**$ 19.13**	**1.000**	**$17.73**	**1.000**	**$18.49**	**1.000**	**$17.91**	**1.000**	**$ 20.34**	**1.000**

Note. n=199,559 across all five years of the study period. The sample sizes for flu season 2010-2011 through 2014-2015 were 40,017, 39,534, 42,056, 40,037, and 37,915 respectively. All costs are representations of total reimbursed and are in 2017 U.S. dollars. "%" column represents the percent each vaccination was administered compared to all influenza vaccinations in the corresponding year.

Clinician costs associated with vaccine administration were also taken directly from the claims data. CPT code 90471 is used specifically for a single injection of a vaccine. It should be noted that this figure was considerably higher than the cost produced by Bridges *et al.* in 2000, who multiplied an estimate of the administering clinician's salary by 0.25 hours.

Finally, this model includes a measure of productivity lost by the vaccine recipient. Bridges *et al*. estimated the time lost to be 30 minutes. This research multiplies the average Vermont wage in each study year by .5 hours to estimate the total cost of lost productivity.

The costs were then summed and multiplied by each year's vaccination rate (V), which is taken directly from the CDC's immunization registry, which reports the number specifically for 18-64-year-olds. This produced the cost per Vermonter for influenza vaccination that is used in the model. The Vermont Vaccine Purchasing Program supplies vaccines only to primary care providers. Because of this, not all administers of the vaccine received the reduced dosage price that the CDC provides to government purchasers. The dosage component of the vaccine cost in the intervention side of the model ($VCost_1$) was weighted using BRFSS survey data. Because the survey only

included a question about vaccination provider in three of the five study years, linear estimates were used for the remaining two years (2012-2013 and 2013-2014). Individuals who received their vaccination from clinics, hospitals, or doctor's office were considered to have been vaccinated by a primary care provider and received the reduced rate in the intervention.

The cost of treatment (TCost) was calculated using similar methods, but the equation included more variables, including the imbedded SIR model. Medical costs were queried from VHCURES medical claims data. The query divided the data into the same flu seasons used to determine vaccination costs, then identifieed claims with an influenza-specific International Statistic Classification of Diseases and Related Health Problems (ICD) code. These codes differ from the CPT codes used in that they identify diagnoses (influenza), rather than procedures (vaccination). Because many cases of influenza go undiagnosed, these costs can only be applied to the percent of infected individuals who are medically attended, which is extrapolated from CDC data. Other research has used codes for influenza, influenza-like illness, and upper respiratory infection, but this research uses only influenza ICD codes: 487, 4870, 4871 and 4878. Every medical claim with any indication of an influenza diagnosis was identified. Again the list was then reduced to include only claims paid by commercial insurers and exclude patients over the age of 65 or under the age of 18, individuals residing out of state, and claims that were denied by the insurer – the same criteria used to identify vaccination claims. Once the claims had been identified, the total reimbursed for all claim lines was summed to capture the medical treatment cost of influenza. This insured that all

procedures associated with the influenza diagnosis were included in the total medical costs.

Not all influenza cases are treated by medical personnel. In fact, most influenza cases do not have a clinician encounter at all. To capture the medical costs per Vermonter, it was necessary to estimate the percentage of influenza cases that were medically attended. This figure is calculated from CDC data. The CDC estimates medical visits and total influenza cases each year – the ratio of these two figures is the percent medically attended. Unfortunately, there is no state-specific data on influenza.

The cost of over-the-counter medications has previously been estimated at $3 per patient (Molinari, 2007). This figure was adjusted for inflation and included in the treatment cost variable. Lost productivity due to influenza has been assumed to be two days. Vermont Department of Labor wage data was used to estimate the average wage loss. Pharmaceuticals (typically to mitigate pre-existing conditions exacerbated by infection) were estimated at $49.38 per medical patient in the literature (Bridges, 2000), and adjusted to $72.98 2017 U.S. dollars. This too was multiplied by the percent of medically attended.

All treatment costs were then summed and multiplied by the percent of the population infected by year, which is generated by the SIR model. This produced the average treatment costs for commercially-insured 18-64-year-old Vermonters. The average treatment costs were added to the average vaccination costs to produce the average cost of influenza per commercially insured 18-64-year-old Vermonter.

Table 5: Cost analysis variables by year for Vermont

	Variable	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015
	Historic					
VCost	Dosage (Historic Price)	$ 19.13	$ 17.73	$ 18.49	$ 17.91	$ 20.34
	Clinician	$ 24.34	$ 23.84	$ 25.91	$ 27.73	$ 29.58
	Productivity	$ 11.39	$ 11.24	$ 11.12	$ 11.13	$ 11.52
	Administration	$ -	$ -	$ -	$ -	$ -
VRate	Vaccination Rate	0.389	0.365	0.411	0.421	0.412
TCost	Medical Care	$ 345.84	$ 401.35	$ 566.15	$ 739.78	$ 513.42
	Pharmaceuticals	$ 72.98	$ 72.98	$ 72.98	$ 72.98	$ 72.98
	Medically Attended Influenza	41.3%	40.8%	40.9%	38.8%	41.3%
	Medicine	$ 4.01	$ 4.01	$ 4.01	$ 4.01	$ 4.01
	Productivity	$ 364.50	$ 359.52	$ 355.82	$ 356.26	$ 368.58
TRate	SIR Infected %	6.5%	9.6%	8.4%	7.4%	19.0%
	Intervention					
VCost	Dosage (Historic Price)	$ 19.13	$ 17.73	$ 18.49	$ 17.91	$ 20.34
	Dosage (VVPP Price)	$ 9.29	$ 11.95	$ 11.75	$ 11.58	$ 12.27
	PCP Administerd Vaccienes	62.9%	60.8%	52.0%	48.7%	47.8%
	Weighted Dosage Price	$ 12.94	$ 14.22	$ 14.99	$ 14.82	$ 16.49
	Clinician	$ 24.34	$ 23.84	$ 25.91	$ 27.73	$ 29.58
	Productivity	$ 11.39	$ 11.24	$ 11.12	$ 11.13	$ 11.52
	Administration	$ 0.34	$ 0.44	$ 0.43	$ 0.43	$ 0.45
VRate	Vaccination Rate	42.8%	40.2%	45.2%	46.3%	45.3%
TCost	Medical Care	$ 345.84	$ 401.35	$ 566.15	$ 739.78	$ 513.42
	Pharmaceuticals	$ 72.98	$ 72.98	$ 72.98	$ 72.98	$ 72.98
	Medically Attended Influenza	41.3%	40.8%	40.9%	38.8%	41.3%
	Medicine	$ 4.01	$ 4.01	$ 4.01	$ 4.01	$ 4.01
	Productivity	$ 364.50	$ 359.52	$ 355.82	$ 356.26	$ 368.58
TRate	SIR Infected %	5.7%	8.6%	7.4%	6.5%	17.9%

Note. 2017 US dollars.

2.3. Cost analysis – Intervention Variables

The same methods are used in the intervention side of the cost analysis model with very few changes in the values used. It's important to note here that the creation of a universal influenza vaccination program will likely entail different statutes, laws, and regulations depending on the population served. In the case of Vermont, the means of vaccination distribution is the Vermont Vaccine Purchasing Program (VVPP), which is mandated by state statute to "purchase vaccines from the federal Centers for Disease Control and Prevention at the lowest available cost." (Act 191, 2006). This has implications for Vermont's implementation of such a program that might not be experienced in other scenarios. It means that all dosage prices would be lowered to the CDC's cost per dose, which is represented in Table 5.

Table 6: CDC Cost per dose by year

Vaccine	CPT	2014-2015	2013-2014	2012-2013	2011-2012	2010-2011
Afluria (IIV3) multi-dose vial	90658	$ 6.53	$ 7.82	$ 8.25	$ 8.25	$ 8.25
Fluzone (IIV4) single-dose vial	90686	$ 13.58	$ 9.93	$ 10.53	$ 10.97	$ 10.97
Afluria (IIV3) single-dose syringe	90656	$ 7.29	$ 8.13	$ 9.00	$ 9.00	$ 9.00
Afluria (IIV4) multi-dose vial*	90688	$ 11.35	$ 11.35	$ 11.35	$ 11.35	$ 11.35

Table 6 shows the prices taken directly from CDC's website. They reflect the CDC contract price for each influenza vaccination in January of the respective flu season. The vaccination costs were weighted according to the frequency with which each was administered, and the weighted average cost was used as the dosage cost in the VCost variable of the cost-analysis model. The weighted averages used can be found in Table 4 and range from $9.29 during the 2010-2011 flu season to $12.27 during the 2013-2014

season. This resulted in a reduced cost-per vaccination. The lost productivity of the patient and the cost of the clinician are assumed to be the same as in the historical data.

Another small difference is the cost of administering the VVPP program itself. The current contract with KidsVax – the third party through which the VVPP is run – calculates the administration cost as 2.7% of the dosage price. That expense varies year to year, is included in Table 4, and is added to the VCost of the intervention portion of the model.

The final variation between the historical and intervention variables comes from anticipated increases in adoption rate, and the effects of this increase on the non-vaccinated population. The Vermont Department of Health's immunization program chief estimates a 10% increase in vaccination rates once the vaccines become available to all Vermonters, free of charge. The SIR model is used to calculate the effects of this increase in vaccination rates on the instances of influenza in the state of Vermont. In each of the five study years, the vaccination rate provided by the CDC's registry was increased by 10%, with the additional vaccinations being distributed according to the figures queried from the VHCURES claims data. The Vermont Department of Health's Immunization Chief believes 10% to be a conservative increase – it is conservative compared to the increase associated with Rhode Island's influenza vaccination program: 20.7% over four years.

This increase in vaccines administered reduces the infected population in two ways. First, it increases the effective vaccination rate, moves more individuals from the susceptible category to the resistant category – in SIR modeling, vaccinated individuals

are moved from the susceptible to resistant category at a rate in line with the vaccine effectiveness. They are resistant, and no longer susceptible to the disease, nor are they infected and able to transmit it on to others. Second, because there are fewer infected individuals in the infected category at any point in time, there are fewer instances of viral transmission between the infected and susceptible individuals.

CHAPTER 3: RESULTS

If the State of Vermont had included influenza in its Adult Vaccination Purchasing Program for the five flu seasons between fall 2010 and summer 2015, the total economic burden associated with influenza would have been reduced by 6.2%. These societal savings are leveraged chiefly from two mechanisms. First is the drop in dosage price associated with the inclusion of the vaccination in the VVPP. The average cost to vaccinate a Vermonter falls by 12.31% when purchased directly from the CDC at the CDC contract rate – this difference includes the additional cost of administration. By holding the rate of vaccination (and the entire SIR mode) constant and changing only the vaccination cost variable, the five-year average influenza-associated cost to Vermonters falls by 1.7%.

The remaining savings are experienced through the assumed increase in vaccination rate. Vermont immunization officials estimate this increase to be about 10% due to increased supply of vaccines (there would be no charge to providers in the VVPP) and the removal of economic barriers. Without including the indirect benefits of vaccination (herd immunity) a *ceteris paribus* increase in vaccination rate does *not* yield societal savings – the increase in the cost of vaccinating a society is not offset by treatment savings because there is no decrease in chance in infection among the unvaccinated. However, when the indirect effects are included, the additional reduction in treatment costs render the program cost-effective. Accounting for only the change in vaccination rate (and associated SIR model results) the five-year average cost of flu falls by 4.3%.

Table 7 depicts model inputs and results for each of the study years. The *historical* variables are estimates of the actual influenza costs, per Vermonter, for each of the study years. The *intervention* variables depict the altered cost in each of the years. The individual results from each year are included, along with a weighted average for all five study years. Each individual year was weighted by the population of Vermonters aged 18-54. Influenza cost per Vermonter is a calculation of influenza costs to all Vermonters, not just sick Vermonters – the dramatic increase during the 2014-2015 season is due to more Vermonters contracting the virus, and not due to the virus being expensive to treat on a case-by-case basis.

Table 7: Simulated cost analysis results

Variable	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	Weighted Average
Historic						
Vaccination Rate	38.9%	36.5%	41.1%	42.1%	41.2%	39.9%
Vaccination Cost	$ 54.86	$ 52.80	$ 55.52	$ 56.77	$ 61.44	$ 56.26
Vaccination Cost Per Vermonter	$ 21.34	$ 19.27	$ 22.82	$ 23.90	$ 25.31	$ 22.51
Treatment Rate	6.5%	9.6%	8.4%	7.4%	19.0%	10.2%
Treatment Cost	$ 541.52	$ 556.88	$ 621.38	$ 675.75	$ 614.84	$ 601.74
Treatment Cost Per Vermonter	$ 35.42	$ 53.57	$ 51.95	$ 49.74	$ 117.06	$ 61.35
Influenza Cost Per Vermonter	$ 56.76	$ 72.84	$ 74.77	$ 73.63	$ 142.38	$ 83.86
Intervention						
Vaccination Rate	42.8%	40.2%	45.2%	46.3%	45.3%	43.9%
Vaccination Cost	$ 49.01	$ 49.73	$ 52.46	$ 54.11	$ 58.04	$ 52.64
Vaccination Cost Per Vermonter	$ 20.97	$ 19.97	$ 23.72	$ 25.06	$ 26.30	$ 23.18
Treatment Rate	5.7%	8.6%	7.4%	6.5%	17.9%	9.2%
Treatment Cost	$ 541.52	$ 556.88	$ 621.38	$ 675.75	$ 614.84	$ 601.74
Treatment Cost Per Vermonter	$ 30.89	$ 47.72	$ 45.98	$ 43.65	$ 110.20	$ 55.50
Influenza Cost Per Vermonter	$ 51.87	$ 67.68	$ 69.69	$ 68.71	$ 136.51	$ 78.68
Savings Per Vermonter	**$ 4.89**	**$ 5.16**	**$ 5.07**	**$ 4.92**	**$ 5.87**	**$ 5.18**
	8.6%	7.1%	6.8%	6.7%	4.1%	6.2%

Note. All Per Vermonter figures are representations of commercially insured 18-64-year-old Vermonters.

As expected, potential savings vary from year to year depending on several factors. Chief among these is the effective coverage (EC) rate, calculated by multiplying

the vaccination rate (V) by the vaccination effectiveness (VE). The 2010-2011 season, for example, had a high EC of 23.3% (38.9% vaccination rate and 60% vaccine effectiveness) and resulted in potential savings of 8.6%. On the other hand, the EC in Vermont during the 2014-2015 flu season was only 7.8%. This is due to a largely ineffective vaccine (VE = 19%) which offset a relatively high vaccination rate (V = 41.2%) and resulted in the lowest savings (4.1%) of all the study years.

Some of the most important findings resulting from this research are the dynamics between the various variables in the model. Sensitivity analysis can help illustrate the interdependence of variables, and how each of them relate to the cost-benefit of vaccination. This sensitivity analysis was conducted by re-running the model with and adjusting only one variable each time. By holding the rest of the model constant, we gain a better understanding of the magnitude each component has on the resulting savings.

Table 8: Sensitivity Analysis

Variable Name		Variable			Results (% 5-year Savings)		
SIR Variables							
Coefficient of Transmission (+/- 5%)	β	0.529	0.557	0.585	25.5%	6.2%	-21.8%
Coefficient of Recovery (+/- 5%)	γ	0.408	0.429	0.450	7.9%	6.2%	4.4%
Reproductive Rate (+/- 5%)	*Ro*	1.235	1.3	1.365	25.5%	6.2%	-21.8%
Intervention Vaccination Increase (+/- 5%)	*Vi*	0.05	0.1	0.15	4.1%	6.2%	8.0%
Vaccine Effectiveness (+/- 5%)	*VE*	-5%	-	+5%	2.5%	6.2%	9.6%
Cost-Effectivenss Variables							
Vaccination Cost (+/- 10%)	*Cost*	-10%	-	+10%	6.4%	6.2%	5.9%
Treatment Cost (+/- 10%)	*Cost*	-10%	-	+10%	5.9%	6.2%	6.4%

Note. The center figure for each variable was the number used in the final version of the model. The number to the left and right represent variations to that variable, the corresponding savings can be found under the *results* header of the table.

Table 8 shows sensitivity analysis for some of the variables included in the model. The same coefficient of transmission, coefficient of recovery, reproductive rate, and interventional vaccination increase were used in all study years; this analysis adjusted

that variable the same amount in each of those years. For variables which changed from year to year (vaccine effectiveness, vaccination cost, and treatment cost) a percentage change to the variable was applied. This model was not sensitive to changes in vaccination cost and treatment cost – a 10% change had to be used in order to display a difference in the resulting 5-year savings.

The variables with the most dramatic effect on the results were the coefficient of transmission and the reproductive rate of the virus. These two variables are very related. The coefficient of transmission represents the rate at which infected individuals pass the virus on to susceptible individuals in the SIR model. It is calculated by multiplying the reproductive rate by the coefficient of recovery. Even a slight increase in the infectiousness of a disease has substantial effects on the cost-benefit of a vaccination. A more contagious virus is harder to treat by vaccination in a population because the unvaccinated individuals can infect a higher number of unvaccinated individuals – the marginal benefits of each person vaccinated are diminished. There is little that can be done by public health or medicine to alter either of these variables.

The coefficient of recovery has a similar but lesser effect on the cost-benefit of a vaccination program. If the coefficient of transmission controls the flow from the susceptible compartment to the infected compartment, the coefficient of recovery can be thought of as determining the flow of the infected compartment to the recovered compartment. The faster individuals move to the recovered compartment, the less time they must spread the virus to the susceptible individuals. Perhaps counteractivity, a higher coefficient of transmission, results in a reduced marginal benefit for additional vaccinations. This is because the less time infected individuals must spread the virus, the

lower the treatment cost is, per Vermonter – fewer people get sick. If the treatment cost is lower relative to the vaccination cost, the cost of vaccination individuals is not as heavily offset by the treatment savings. The CDC suggests that antiviral drugs can lessen the time an individual is sick by one or two days – but also create additional costs and only affect individuals who have been prescribed them and not the population as a whole.

Unsurprisingly, an increase in the uptake of vaccinations due to the implementation of the program results in a more cost-effective program. If, for example, vaccination rates increase 15% instead of 10% statewide, the 5-year average savings would grow from 6.2% to 8.0%. Influenza vaccination programs should invest considerably in educational campaigns and access-issue resolutions. The potential for return on investment is appealing.

Vaccine effectiveness also increases the economic benefits of inoculation. When vaccine effectiveness increases, so does the cost-benefit of the program. A more effective vaccine increases the effective coverage rate, transitions more individuals directly from susceptible to resistant, and enhances both the direct and indirect effects of vaccination.

Variation in the total cost of vaccination and treatment also affects the economic outcomes of the model. What is interesting is that even relatively large variances in these variables don't alter the cost-benefit of the model to a large degree. Not surprisingly, lowering the cost of a vaccine increases the effectiveness of the program. Lowering the cost of the treatment does not.

The variables used in this model were either calculated from universal claims data, taken from CDC or BLS databases, or derived from literature and chosen to fit historical norms. Although the sensitivity analysis has shown that small variation in some

variables can dramatically affect the outcome of the model, they also change the model outcomes so that they no longer fit within the literature. From this research, a universal influenza vaccination program could be cost-effective for the State of Vermont. Additional savings would result from higher vaccination rates, which should be encouraged through various means.

CHAPTER 4: LIMITATIONS

Like all models, this cost-benefit analysis is not without its limitations. In all instances an attempt was made to provide conservative estimates of the cost-saving potential of a universal vaccination program.

Vaccine effectiveness varies by age and health status. As addressed earlier in this paper, the vaccine effectiveness is lowest in the elderly and the highest in children and young adults. The VE variables used in the model are averages for the entire population. Because the model includes only working-aged adults, this might be an underestimate of vaccine effectiveness – unfortunately, the CDC does not calculate VE for different age cohorts. Similarly, the basic reproductive rate R_0 varies between different age cohorts. This is due to both physiological and sociological differences. As addressed earlier, studies have shown the R_0 of elderly populations to be lower than that of children and young adults. This research uses an average of 1.3, but it might be an underestimate of the reproductive rate in the study population. Both variables were kept at their societal average to provide conservative estimates of potential savings.

In the literature, work absenteeism was calculated at anywhere from .5 to 3.8 days. This research uses 2 days to control for the confusion of "days ill" and work absenteeism. If an individual is sick on the weekend, for example, there is no associated lost productivity. It should be noted that there is no agreement as to what this variable should be.

This paper uses a susceptible-infected-resistant (SIR) model to model the transmission of infectious disease instead of a susceptible-exposed-infected-resistant

(SEIR) model. The SEIR model includes an extra coefficient of time between exposure to a pathogen and infection by that pathogen to account for the incubation period of the virus. Future research could examine the impact of the inclusion of the incubation period in the model.

Although claims data remains one of the most fully comprehensive sources for health care information, it is now without its drawbacks. The VHCURES data is a compilation of data from all providers and insurers in the state of Vermont uploaded and unified in a database. The data is only as good as its sources, and the skill of those compiling it. It can be unruly and sometimes inaccurate – typically the law of large numbers reduces the impact of any irregularities, but in a state as small as Vermont the impact of an error might be more significant. VHCURES data was made available through the Green Mountain Care Board (GMCB). All query results, figures, and analyses are from this research and not necessarily those of the GMCB.

Some variables in this model are based off survey data. Self-selection bias, and recall bias are limitations in all self-reported survey data. Although not a limitation per-se, special care is necessary when conducting an economic evaluation of a public health topic. This research intentionally avoided socioeconomic classification of the population. Because workplaces absenteeism is a measure of lost wages, the economics of vaccination vary widely when the population is stratified by household income. All health economic research must be careful to remain ethical when dealing with socioeconomic class. It is for this reason that – aside from average VT wage – income was not considered in the model, or when discussing selective vaccination programs. A future iteration of this model, however, could look at the marginal value of wages lost.

While it is true that quantifying work absenteeism of a high-earner results in a larger economic loss to society in terms of GDP, it does not take into account the marginal value of those earrings relative to the worker who earned them. Many wealth individuals can easily (finically, at least) afford to be sick while lower wage-earners would struggle to adjust for two days of lost earnings. Paid sick leave is a benefit that may not even be available to the poorest of Vermonters or the self-employed. In order to better incorporate health and economic equity into policy and public health decision, considerations must be made to account for differences in earnings and socioeconomic status.

This research is a study of inter-pandemic, or seasonal influenza. It is a retrospective study that reviews data from past flu seasons. The five years included in this study are in line with expectations for seasonal flu infection rates. This study does in no way accounts for flu pandemics, so called “black sawn” events, or other outliers. Flu pandemics have historically been treated separately in the literature, and pose a rare but severe risk to populations requiring different epidemiological analysis. Pandemic flu has been excluded from this research.

Finally, this is largely a quantitative paper and therefore somewhat reductive in its analysis. Economics, and in particular health economics must be mindful of the importance of human nature. This paper does not account for the value of a life-year added, or the willingness-to-pay for avoidance of influenza symptoms. Including such variables would necessitate a much more comprehensive project, through their admission must be noted as a limitation.

CHAPTER 5: DISCUSSION

Seasonal influenza is an annual, global public health risk. Each year, tens of thousands of people die from the infection and hundreds of thousands more are hospitalized. While children and seniors are most at risk for serious complications, the virus is indiscriminate, and can infect up to 26% of the entire population in a given year.

Although healthy adults do not see the same increase in influenza-associated mortality as older and younger cohorts they can act as a vector, aiding the virus as it moves among at-risk populations. Each season, influenza may be transferred from children in child care and schools to the elderly via the parents and caretakers of the youth. An intervention among 18-64-year-old adults not only reduces their risk of infection, but that of the entire public.

Vaccination is a potent mechanism for this intervention, although the effectiveness in any given year can vary. Depending on the year, vaccination can decrease the chance of infection from anywhere between 10% to 60% (CDC, 2017). Vaccination rates, too, vary dramatically by age, location, education, and socioeconomic factors.

Despite these variations in both vaccine and population, evidence suggests that vaccinating all persons over six months old is cost-effective. Insurers and patients would certainly benefit from such a program. Insurers benefit because cost of the vaccine dose included in the VVPP assessment would be less than the private-market price currently available to providers and a higher vaccination rate means a reduction influenza-related-

illness claims; patients benefit because they will be able to receive the vaccination free-of-charge from primary care providers and will be less likely to become sick. It is unclear if providers will benefit financially – although it will be easier for them to maintain an adequate supply of vaccinations, revenue from flu vaccinations might outweigh the cost to providers in the current system. More research is necessary to fully understand the impact of an influenza vaccination program on providers.

Furthermore, the associated reduction in influenza-like illness hospitalizations and mortality alleviates the strain on medical systems and frees up facilities and clinicians to focus their attention elsewhere. Since 2010, the CDC's Advisory Committee on Immunization Practices has recommended all Americans six months and older receive an annual flu vaccination. Simultaneously, national and state-level health assessment plans have set target flu vaccination rates of 80% for adults.

Research conducted as part of this study has corroborated the literature and recommendations from the CDC. The epidemiological cost-benefit model outlined in this document has demonstrated that a more highly vaccinated population would have resulted in considerable savings in Vermont's health economy (all direct and indirect economic activity affiliated with the health care system) over the five flu seasons occurring between fall 2010 and summer 2015. A 10% increase in vaccination rates in any of the evaluated years, with reductions in the cost of vaccines, would have resulted in savings without any other intervention.

The Vermont Vaccine Purchasing Program (VVPP) – a state mandated program – includes all CDC recommended vaccines for adults except influenza. The state statute

requires that all vaccines included in the program be purchased at the lowest possible rate and made available for order at no cost from Vermont primary care providers enrolled in the program. Funding for vaccines is provided by health insurers.

If influenza vaccines were included in the VVPP, there would be two beneficial effects for residents, insurers, and the population. First, the vaccines would be purchased at a considerably lower cost, resulting in savings; and second, the reduction in cost would increase access to the vaccine. Although access to care is itself a complicated issue, suppliers of the vaccine would be able to keep a larger supply on hand without fear of over-purchasing the product. At the same time, residents whose chief barrier to vaccination was financial would now be able to receive a flu shot at no direct expense to them. Because of these two factors, officials at Vermont's Immunization Program estimate flu vaccination rates could increase over 10%. At the recommendation of the VVPP board, and the judgment of the Vermont Department of Health, influenza can be included in the Adult Vaccine Purchasing Program and Vermont can make a large stride towards achieving its public health goals.

There are several courses of action that can be taken with this information. The first is to maintain the status quo and continue to allow market forces and *homo economicus* to distribute vaccinations without intervention. There is little reason to expect vaccination rates for working-aged adults to climb higher than 50% without some sort of program and achieving the federal goal of 80% of the adult population vaccinated would be unattainable.

A second option is to expand awareness of the benefits of vaccination through education, outreach, and marketing programs. Because vaccination is cost-effective, funds contributed to this cause would benefit the public health of a population while reducing the economic burden of seasonal influenza. As demonstrated in this research, a 10% increase in adoption rates among 18-to-64-year-olds is cost-effective even when all other variables are held constant.

The third and most involved option would be to include influenza vaccinations in the adult vaccination program. The VVPP would add influenza to the current suite of vaccinations and provide them free of charge to Vermont primary care providers for use in all patients. The added cost of the flu vaccine would be included in the per-member per-month assessment charges to health care insurers and received by the State of Vermont. This option has the most potential for savings. The reduction in dosage price also serves to mitigate downside risk by reducing the financial burden of supplying the vaccine to providers.

This research has uncovered other questions deserving of their own studies. It is clear that when accounting for the indirect effect of vaccination (herd immunity), economic and public health benefits associated with higher vaccination rates are increased. This finding aligns nicely with the federal and local vaccination goals and begs the question: *how do we increase vaccination rates*? Vermont's public health officials typically group their initiatives into three categories: public education; regulations and policy; and health access. Each of these three approaches could increase vaccination rates.

As addressed above, a public education campaign could be created by the Vermont Department of Health with the goal of informing the population of the personal and societal benefits of vaccination. Historically, public educations campaigns have been quite expensive and have not had much of an impact on vaccination rates. This could be because of discounting rates and optimism bias. For many, it may be hard to part with the up-front cost of vaccination because there is a chance of greater costs in the future. What is not known is whether a lack of education about influenza vaccination is the reason for the low adoption rates. Perhaps an incentive program paired with an education campaign could increase vaccination rates. Such a campaign would likely have to be tailored to fit the needs of each individual community. For example, some regions of Vermont might need to be made aware of the public health benefits of vaccination while others would need to be informed that it is being provided free-of-charge. Regardless, there is no guarantee of the effectiveness of a marketing campaign in isolation. However, increasing the public's knowledge about vaccination is likely a necessary complementary component to either a regulatory or access-increasing approach.

The second option – increasing vaccination rates through regulations and policy – would certainly be cost-effective but potentially controversial. Vermont's immunization program management is well aware of the resistance to required vaccination. The influenza vaccination does not have to be a population-wide initiative. The state could introduce policy that would require only certain individuals to be vaccinated. Ideally this would include adults who spend considerable time with high-risk populations and those with a high likelihood of being a disease vector between various cohorts. Examples

include clinicians, child care providers, teachers, social workers, and those that work closely with older populations.

The third method for increasing vaccination involves increasing access to flu shots for Vermonters. Health care access issues take multiple forms, and Vermont must consider all obstacles to best address the issue. The influenza vaccine may be inaccessible due to transportation, economic, or social hindrances. Providing flu shot at no cost to primary care providers addresses only one of these problems. Policies and public health practices aimed towards increasing access will need to take multiple access issues into account. Perhaps a mobile vaccination unit – similar to a mobile blood-drive or mobile needle exchange operation – could be developed in order to provide vaccines to Vermont's rural regions. The Health Department's district offices could also be called upon to assess the need and plan for the distribution of vaccines across the state. Primary care offices could be financially incentivized to increase their distribution of vaccines by opening free clinics. Future research should survey the unvaccinated population to learn the reasons individuals are not annually vaccinated and develop policy to address those issues.

What is also apparent from this research is that there is a way to reduce the societal and economic cost of seasonal influenza without increasing the vaccination rate at all. The SIR model suggests that there is an optimal time for vaccinating against the flu. This time is likely between October and December. It is evident from the claims data that a healthy large portion of the population receives flu shots after the flu season is already in full swing. This second wave of vaccinations typically happens in January and

could be caused by a shortage in vaccination supply, or as a reaction to widespread infection. Evidence suggests that if individuals who are vaccinated after January 1 were instead vaccinated in the late fall/early winter, the susceptible population would be reduced at an earlier date with no increase to the infected population. Because the flu vaccination takes upwards of two weeks to be effective, many of those receiving the shot late in the flu season do so futilely. Future research could work to identify the optimal months for receiving a vaccination, determine the reasons why individuals receive their shots late in the season, and develop a plan to better align the vaccination of the population with the biologically optimal timeframe. This model is used in this research to test a specific intervention for reducing the economic burden of influenza in the State of Vermont. The model can be adapted for use in many other scenarios that require societal economic modeling of transmittable diseases.

A 10% increase in Vermont's influenza vaccination rate over the five flu seasons between 2010 and 2015 would have created notable economic savings and freed up health care resources across the state. The vaccination rates of the years studied were aligned with rates Vermont typically experiences, and the prevalence of annual infections included in the model mirrored data from the literature, each of which help to validate the findings. Adding influenza to Vermont's Adult Vaccine Purchasing Program would result in further savings due to the reduction in dosage prices. Inclusion of influenza in the VVPP would likely result in a healthier population at a reduced cost.

This paper is intended to be both a community development and applied economics thesis. While the application of economic principles is apparent throughout, it

is important to address the impact of immunization on communities. Public health can be viewed as a public good: individuals acting in their own perceived self-interest can detract from that public good, while emergent benefits (such as herd immunity) can arise from a unified public health endeavor. Achieving optimal health through various policy and regulatory methods is a task that often falls to community and government officials. A healthy population is necessary to keep local networks, relationships, and economies strong, healthy, and efficient. Promoting health improves communities, and immunization against infectious diseases is a proven method of health promotion.

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