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FULL REPORT

SYSTEMATIC REVIEW OF THE COST-EFFECTIVENESS OF INFLUENZA IMMUNIZATION PROGRAMS: A CANADIAN PERSPECTIVE

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CONFLICTS OF INTEREST

During the timing of writing this technical report, ET was an employee of AstraZeneca Canada.

Abstract

In Canada, currently no national seasonal influenza immunization program exists. To better inform policy, the cost-effectiveness of influenza immunization programs was examined.
Using a best-evidence synthesis approach, 31 economic evaluations were reviewed. Subgroups emerged from the literature, including pregnant and post-partum women, children, and healthy adults. Generally, from the societal and healthcare system perspective, vaccination was cost-effective. For pregnant and post-partum women, vaccinating all versus only high risk was cost-effective. For children (6 months to18 years), vaccinating all versus only high risk was cost effective, especially for infants, toddlers, and adolescents. For healthy working age adults (19 to 64 years), results were mixed, and sensitive to vaccine efficacy, uptake, and productivity loss. For adults with co-morbidities and healthcare workers, vaccination was cost-effective.
In Canada, six provinces (AB, SK, MB, ON, NS, NL) and all territories offer universal programs as of 2014. Three provinces (BC, QC, NB) offer programs targeting high risk groups only.

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ABBREVIATIONS

AOM	acute otitis media
BIAs	budget impact analysis
BMJ	British Medical Journal
CAD	Canadian dollars
CADTH	Canadian Agency for Drugs and Technologies in
CBA	cost-benefit analyses
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CinAHL	Cumulative Index to Nursing and Allied Health
CMA	cost-minimization analysis
CUA	cost-utility analysis
DALYs	disability adjusted life years
DARE	Database of Abstracts of Reviews of Effects
EBSCOHost	Elton B. Stephens Co Host
EED	Economic Evaluation Database
EQ-5D	European Quality of Life-5 Dimensions
GBS	Guillain-Barré Syndrome
GP	general practitioner
HIV	human immunodeficiency virus
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ILI	influenza-like illness
LAIV	live attenuated influenza vaccine (intranasal)
LCI	laboratory-confirmed influenza
MeSH	medical subheadings
MMR	measles, mumps, and rubella
NACI	National Advisory Committee on Immunization
NHS	National Health Service
PHAC	Public Health Agency of Canada
PQAQ	Pediatric Quality Assessment Questionnaire
PSA	probabilistic sensitivity analysis
PV	present value
QALYs	quality adjusted life years
RCT	randomized controlled trial
SF-12	Short Form 12-item Survey
SIGN	Scottish Intercollegiate Guidelines Network
TIV	injectable trivalent influenza vaccine
UIIP	Universal Influenza Immunization Program
VAS	visual analogue scale
WHO	World Health Organization

1 INTRODUCTION

This introductory chapter provides background on influenza, describing its impact and importance as a public health issue. The role of vaccines for the prevention of influenza is discussed as well as the current state of provincial immunization programs in Canada. Next, a basic description of health economics is provided, introducing key characteristics of economic evaluations and their relevance to influenza immunization programs. Relevant systematic review methods such as meta-analysis, narrative summary, and best evidence synthesis are discussed briefly. In recognition of the policy differences in Canada, a portion of this section highlights the current provincial influenza immunization programs and the inconsistencies that exist. Finally, specific research questions in addition to the primary and secondary research objectives conclude the section and state the purpose and need for this review.

1.1 Problem Statement

Commonly referred to as “the flu,” influenza is an acute viral infection of the respiratory system, which causes annual epidemics that peak during November to March in countries that are located in the Northern Hemisphere such as Canada.

Individuals infected with seasonal influenza can face a range of health effects, from less severe symptoms such as general malaise, upper respiratory illness, and transient muscle pain, to more complications such as pneumonia and worsening of underlying medical conditions. Severe problems can result in physician office visits, emergency department visits, hospitalizations, and death.

Whether minor symptoms or severe problems, influenza infection results in negative health outcomes that cause loss of productivity. Absences, time off work, and emergency hospitalizations all contribute to great economic losses for the entire population. That said, while most Canadians do not deem the implications of influenza as overly serious, the aggregate outcomes of influenza infections from a public health perspective present a more ominous situation. As with many infectious diseases, provincial governments need to be prepared with carefully designed immunization programs to prevent infection and transmission, mitigate the impact of outbreaks, and reduce any economic losses due to reduced productivity.
In response to the seasonal influenza threat every year, each province and territory in Canada has designed and adopted its own individual approach to immunizing their respective

populations. These publically funded immunization programs vary across the country. Some provinces are more liberal in their coverage criteria. For instance, Ontario provides publically funded influenza vaccine to all residents with the exception of those under six months of age who are unable to receive influenza vaccination at all. Other provinces use criteria to determine who will be provided influenza vaccine. For example, Québec provides publically funded influenza vaccine to only individuals deemed as “high risk.”

Publically funded programs can be generally termed as “universal” or “targeted.” The term universal refers to immunization programs where publically funded vaccine is available for all residents. No specific criteria (such as age, risk, occupation, etc.) are used to restrict a resident from receiving publically funded vaccine. In this case, any resident can request vaccination from their physician, attend large scale public health clinics and receive it from a nurse, or in some provinces, have a community pharmacist administer it at the pharmacy. Mass vaccination clinics are typically held in public meeting places such as community centers, town halls, community pharmacies, schools, and shopping malls.

In contrast, a “targeted” program refers to a “selective” program, where specific criteria are used so that only certain groups of the population receive publically funded vaccine. These select groups are often defined by risk of severe illness age group (children and older adults), and the degree of potential exposure to the virus (e.g. front-line health care professionals, nursing home workers). Those who fall outside of these groups can purchase vaccine from a community pharmacist or physician or pay at public health clinics for the vaccine. From an observation of market dynamics, it appears that patient payment is a barrier to immunization as the majority of patients in Canada rely on the publically funded model to receive influenza vaccine. In total, approximately 90% of influenza immunizations are administered through the publically funded model, demonstrating the impact of public funding on vaccination uptake for a population (IMS Brogan, 2010).

For the purposes of this thesis, immunization programs that provide vaccine to all individuals are referred to as “universal” programs. Immunization programs that use criteria to select specific population groups based on risk are referred to as “targeted” programs.
An important aspect to consider is that unlike immunization policy, the actual influenza virus is not restricted by political borders. The type of program one province selects has an overall effect on the health of residents outside of its provincial borders. The design of an influenza

immunization program has several factors and so provinces create policies in accordance to what suits their needs. One consideration when designing an immunization program is cost-effectiveness. With fewer dollars to allocate to the growing demands of the provincial health care system, cost-effectiveness continues to be an increasingly important parameter in any evaluation of a publically funded health-related activity, including immunization programs.

In light of this economic reality, this thesis examines the literature regarding the cost-effectiveness of influenza immunization programs, using a best evidence synthesis approach, explicit inclusion and exclusion criteria, established quality appraisal tools, and a review of the current provincial and territorial influenza immunization programs. More detail on methods will follow in later sections. The results will provide decision makers additional information on assessing a targeted or high-risk only influenza immunization program versus a universal influenza immunization program.

1.2 The Impact of Influenza

Influenza, colloquially referred to as “the flu,” is highly contagious and easily transmissible. The virus can be transmitted from everyday personal contact such as hand-shaking, sneezing or coughing droplets, or through passing along the virus through fomites such as towels and door knobs (Centers for Disease Control and Prevention, 2013). Close proximity to infected birds and pigs can also be a point of exposure to other forms of influenza. Even though to the elderly and those with other health complications influenza is a dangerous infection, to the majority of Canadians the virus may appear relatively harmless with minor symptoms. However, the reality is that infections are troublesome and dangerous for the entire population. Public health agencies such as the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and in Canada, the Public Health Agency of Canada (PHAC) and the National Advisory Committee on Immunization (NACI), constantly monitor global patterns of infection, review scientific literature, and update immunization policies to help reduce the impact of seasonal influenza. Given that influenza is a worldwide issue and can affect any age group, it is essential that proper policies are in place to avoid potential dangers. From the public health perspective, the effects of influenza can be severe, as an uncontrolled pandemic can harm a nation’s economy through lost workforce productivity, increased health resource expenditures, or worse yet, significant morbidity and mortality across the population. This was seen in the Spanish flu pandemic of 1918 - 1919 and other pandemics including the more recent H1N1 swine flu pandemic in 2009 - 2010 (Taubenberger & Morens, 2012; Dawood et al., 2012)

1.2.1 Mortality, Burden, and Cost to Society

Influenza infects approximately 5 to 10% of the global adult population and 20 to 30% of children every year causing respiratory illness and complications (European Centre for Disease Control, 2009). These influenza infections while troublesome, uncomfortable, and inconvenient, are generally transient and self-limiting in the majority of individuals. Even so, in many other cases the infection and its respiratory complications can be severe or deadly, particularly in infants, children, the elderly, and those with immunocompromising comorbidities such as diabetes or cancer (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014).

In either case, the burden of illness due to influenza, whether a mild infection or a severely complicated one, can be detrimental to all members of the public, as influenza infections impact the well-being of patients, the health care professionals assigned to treating the patient, and exposed family members. And while the impact of influenza is well studied and recognized, the true burden of influenza is still difficult to properly calculate and assess. The reason for this is that influenza infections do not only cause primary illness but also often generate a range of additional health problems which lead to more severe secondary medical complications. Common complications include viral pneumonia, secondary bacterial pneumonia, and worsening of other underlying pre-existing medical conditions (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). Therefore, when attempting to consider the burden of illness due to influenza, one must also include all of the secondary complications and effects that the primary infection had either caused or exacerbated.

It is estimated that in an average influenza season, 10% to 20% of the Canadian population becomes infected with influenza each year (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). Of these infected patients, approximately 20,000 patients will arrive to a hospital with health complications due to influenza. Inclusive of complications due to influenza infection, it is estimated that up to 3,500 Canadians die every year during an average flu season (Schanzer, Sevenhuysen, Winchester, & Mersereau, 2013). In addition to these lives lost, the societal cost and lost productivity due to influenza is also significant. Over 1.5 million effective workdays are lost each year due to absences and reduced productivity while at work and when combined with all of the health care resources required to treat patients with influenza infections, the total cost each influenza season is estimated to cost $1 billion per year in Canada (Molinari N. , Ortega-Sanchez, Messonnier, Thompson, Wortley, & Weintraub,

2007). Immunization is often touted as an appropriate solution to influenza. The vaccine has been shown to be effective over several decades and in several locations around the world, and there is real world experience of influenza immunization programs in Canada. With the cost of the Universal Influenza Immunization Program (UIIP) in Ontario reaching approximately $40 million per year, policy makers should be as informed as possible in considering what approach or program design is optimal under budget constraints to best protect the population against influenza (Sander, et al., 2010).

1.3 Viral Design, Transmission, and Pathogenesis

There are three types of influenza viruses, named A, B, and C; the viruses relevant to seasonal infections are influenza A and influenza B. Influenza A is the virus that most commonly causes annual infections and is classified into several subtypes based on two surface proteins: hemagglutinin (H), which aids in the binding of the virus to host cells, and neuraminidase (N), another protein that allows the budding of the virus from infected cells (Centers for Disease Control and Prevention, 2014).

There are 18 H subtypes of hemagglutinin (H1 to H18) and 11 N subtypes of neuraminidase (N1 to N11) of which H1N1 and H3N2 are recognized to have caused widespread human infection on a regular basis (Centers for Disease Control and Prevention, 2014). For instance, since 1977, the human H3N2 and H1N1 influenza A subtypes have repeatedly contributed to influenza illness to varying degrees each year (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). Influenza B also has H and N proteins, and divided into two lineages, B/Yamagata and B/Victoria and then further divided into strains. To add further complexity, the northern and southern hemispheres often have differing circulating influenza strains.

Transmission of influenza most frequently occurs through personal contact and can infect a susceptible host directly or indirectly. Direct transmission occurs when particles from an infected individual who coughs or sneezes enters the eyes, nose, or mouth of another individual. Indirect transmission refers to contacting contaminated fomites such as towels, doorknobs, or an individual's hands, and then introducing virus into the nose, mouth, or eyes. For example, after hand-shaking, a host could accidentally rub his or her own eyes. The virus then targets the epithelial cells of the respiratory tract. After entering the host, the virus has an incubation period of one to four days, and then symptoms develop including fever, muscle aches, and respiratory

symptoms such as sore throat, coughing and sneezing (Centers for Disease Control and Prevention, 2013).

1.3.1 Influenza Nomenclature

Further complicating the prevention of seasonal influenza is the fact that the circulating virus strains often change each year. Mutations in the hemagluttinin and neuraminidase change the virus over time, with varying degrees. To identify these constantly changing viral strains, the WHO and CDC have created an international naming convention for influenza viruses, accepted by the WHO in 1979 and published in February 1980 in the Bulletin of the WHO(World Health Organization, 1980).

There are several components to the naming convention of an influenza virus:

- Antigenic type: such as “A” or “B” or “C”
- Host of origin: such as turkey, equine (horse), or swine. When the virus originates from a human source, no specific host is written. In the case viruses are isolated from non-living material, the nature of the material is specified, e.g., A/lake water/Wisconsin/1/79.
- Geographical origin: such as Wuhan, California, etc.
- Strain number: provided as a unique identifier
- Year of isolation: this is written as the last two digits if occurred in 19XX, but now is written with all four digits such as “2009”
- For influenza A viruses, the hemagglutinin and neuraminidase antigen description in parentheses, such as (H1N1), (H5N3)

As examples, two fictitious viruses:

- A/turkey/Ontario/61/98 (H8N4) for a virus from turkey origin in Ontario
- A/Sydney/16/2009 (H3N2) for a virus from human origin in Sydney

Throughout the year, the WHO tracks, reports, and monitors the strains that are most likely to emerge and infect the general population. These strains are then carefully selected as the best vaccine candidates for the season and vaccine manufacturers are then informed to produce vaccine against these strains. Trivalent vaccines have two A strains and one B strain included in the vaccine composition, and newer quadrivalent vaccines have an additional B strain in the formulation. The proper surveillance and selection of the strains is essential for the correct

vaccine to be produced each season since the strain of the influenza virus changes quickly over time (Gerdil, 2003).

1.3.2 Antigenic Shift and Drift

Changes in the influenza virus over time effectively produce new strains that may not be recognized by the body's immune system. These transformations of the circulating influenza virus strains are described in two terms: drift and shift. Antigenic drift describes the natural process of continuous incremental changes in the influenza virus over time. Genes coding for surface proteins mutate and proteins change shape and position over time. Previously developed antibodies are unable to fully recognize this “new” influenza viral strain, lowering the ability of the host’s immune system to specifically target and defend against the “new” infection.

Unlike the slower process of antigenic drift, antigenic shift is a sudden, abrupt, and major change in the influenza virus. A shift describes the creation of a new influenza subtype consisting of hemagglutinin and/or neuraminidase proteins, arising from animals such as birds or pigs; this new strain may be capable of infecting humans and spreading from person to person (Centers for Disease Control and Prevention, 2011). Occurrences of antigenic shift are rare but produce extreme effects. A recent example occurred in the spring of 2009when the H1N1 influenza virus was infecting individuals. In cases of antigenic shift, as in 2009, many people did not have the protective antibodies and were susceptible to infection. Antigenic shift effectively may leave a nation’s population vulnerable to infection and high levels of transmission.

1.3.3 The Need for Vaccines

With constant antigenic drift and the occasional shift, completely eradicating the circulating influenza virus is not likely a feasible option in the near future. Instead, the primary focus of public health agencies is on reducing the effects of the circulating strain by preventing infection and widespread transmission. To reduce the susceptibility to infection both global and local public health agencies emphasize that vaccination is the most effective way to prevent influenza infection (World Health Organization, 2009). Influenza vaccines are designed to expose the recipient to a weakened or dead version of the selected strains of influenza virus. These vaccines often contain the virus in an inactivated or attenuated state such that the recipient is able to achieve an immune response and generate specific antibodies, without actually becoming infected. This process allows the recipient to develop antibodies and effectively

become immune to the specific strains expected to circulate in the upcoming season. Not only does immunity through vaccination reduce the likelihood of infection, but it may also lessen the severity of disease even if infection occurs (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014).

Formulation of the influenza vaccine is performed annually. After announcement of the selected strains by the WHO in late February to early March, vaccine manufacturers begin the process of producing batches for use in the late autumn. In the current Canadian market, most vaccines are trivalent, meaning that they are comprised of two human influenza A subtypes, with quadrivalent vaccines containing two influenza A subtypes and two influenza B subtypes now recently available in Canada. Which strains are included depends upon the representative seed strains declared by the WHO. Most years, one or more of the strains in the vaccine changes from the previous year, though in some years all of the strains are the same as the preceding year. Manufacturers are provided with seed strains based on these WHO selected viruses. Any seasonal changes due to drift and shift identified by the WHO require a reformulation of the vaccines.

Between when the WHO selects these strains and the upcoming flu season, the circulating strain may have changed which could affect the effectiveness of the vaccine. While antibodies produced to protect against a specific influenza subtype are unlikely to provide the same level of protection against other subtypes, there is still the possibility of cross-protection against drifted strains within the same subtype. The amount of protection depends on the degree of drift between the vaccine strain and the circulating strain (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014).

Even though these protective qualities of vaccination appear beneficial, there are also concerns about mass vaccination. The influenza vaccine itself has been implicated in common adverse events such as localized pain and swelling of the skin or tissue where the intramuscular injection occurred. Intranasal vaccines also have been associated with runny nose and nasal congestion. However, more concerning are the systemic adverse events that can compromise the immune system or result in a dangerous anaphylactic reaction. Public health officials are very aware of Guillain-Barré Syndrome (GBS), a condition where an auto-immune response with antibodies generated from the vaccine cross-react with nerve cells. GBS may result in paralysis, permanent nerve damage, or even death. Although GBS is extremely rare and has

not been directly associated with influenza vaccine in recent years, individuals who received the 1976-77 season swine flu vaccine did show an associated increased risk of GBS; however, no causal link was established. The increase in risk was approximately one additional case of GBS per 100,000 people (Centers for Disease Control and Prevention, 2012). Newer emerging evidence in fact suggests that the risk of GBS in fact, is lower in the vaccinated population than in the non-vaccinated population (Kwong, et al., 2013).From a public health perspective where several thousands of individuals are vaccinated, even a slight increase in risk needs to be weighed against the benefits of the vaccine.

1.4 Influenza Risk Groups

While public health agencies agree that immunization is an important and effective method of prevention against infection, deciding exactly who should receive publically funded vaccine differs. Populations are diverse and can be stratified according to the risk of exposure to influenza and susceptibility of resulting complications. In Canada, NACI divides the population into general priority groups with regards to influenza immunization, shown in Table 1.

There are three groups that NACI highlights to immunize against influenza:

- individuals at high risk of influenza-related complications or hospitalization
- individuals capable of transmitting influenza to those at high risk of influenza-related complications or hospitalization
- others

Table 1: Priority Groups for Immunization

Specific populations*	Examples
Individuals at high risk of influenza-related complications or hospitalization	• adults and children with chronic health conditions • morbidly obese individuals • residents of nursing homes or chronic care facilities • people≥ 65 years of age • children 6-59 months of age • pregnant women • aboriginal peoples

*Adapted from NACI Statement on Seasonal Influenza Vaccine for 2014-2015.

Table 1: Priority Groups for Immunization, continued

Specific populations*	Examples
Individuals capable of transmitting to those at high risk of influenza-related complications	• health care providers in facilities and community settings • household contacts of high-risk persons and of infants <6 months of age • caregivers of children ≤ 59 months of age • individuals providing services in closed settings to those at high risk (e.g. crew on a ship)
Others	• emergency service workers including paramedics, firefighters, police officers, national armed forces • People in direct contact during culling operations involving poultry infected with avian influenza • Healthy persons, 5 to 18 years of age, and 19 to 64 years of age are also recommended for vaccination

*Adapted from NACI Statement on Seasonal Influenza Vaccine for 2014-2015.

These are groups of people who are a priority for vaccination programs in Canada (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). NACI also recognized there is benefit to immunizing healthy persons both from 5 to 18 years of age and 19 to 64 years of age in addition to the typical high risk groups, recommending that these healthy persons also be provided vaccination. Widespread illness and societal costs also occur with seasonal influenza in people who may not be traditionally considered at high risk.

In the 2014 – 2015 statement, NACI recommended that additional evidence, such as more extensive data on burden of illness, cost-effectiveness, and programmatic aspects be reviewed to better inform decisions at the provincial or local level with respect to publicly funding influenza vaccine for healthy 5 to 64 year olds or implementing universal influenza immunization programs (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). Since these are only recommendations from NACI, provinces ultimately create their own individualized programs, resulting in some choosing a universal program and some targeting only certain high risk groups.

Traditional risk group stratification is supported by evidence, as rates of influenza infection are highest in children and adolescents (Munoz, 2002). Not only are the infection rates highest in this group, but children and adolescents also play a major role in the transmission of influenza to others. Their proximity to other children in daycare, adolescents in schools, parents and caregivers at home, and potentially elderly grandparents during visits can conceivably be a

significant transmission risk. Immunizing young children and adolescents imparts indirect protection to the household and other members of the community (Whitley & Monto, 2006). When considering the other end of the age spectrum, it is also logical to categorize elderly adults and seniors as a high-risk group, as rates of serious illness and death are highest in older persons (those > 65 years) and typically, older adults are persons with underlying medical conditions as well (Schanzer, Sevenhuysen, Winchester, & Mersereau, 2013). Older persons are often burdened with other comorbidities and are especially vulnerable.

Caregivers, health care professionals, and those in close proximity to children and the elderly are categorized as a priority to reduce transmission to those of high risk of complications. In addition, those who provide essential community services are also a priority to be immunized. The losses the community could potentially face without these workers could deeply impact the proper functioning of community services. Several studies have found that absenteeism of essential health care workers has an impact on the entire community (Saxén &Virtanen 1999; Carman et al., 2000; Wilde et al., 1999).

1.4.1 Herd Immunity

One concept that supports the idea of immunization across an entire population is herd immunity. Also referred to as “community immunity,” herd immunity is a phenomenon in which indirect protection is bestowed across a population by immunizing a proportion of that population (National Institute of Allergies and Infectious Diseases, 2010; Fine, Eames, & Heymann, 2011). Individuals who are not immunized may still be protected against infection because of others in the population who are immunized. Those who are immunized are less likely to become infected and therefore do no spread the infection to others. The proportion of the population that needs to be vaccinated for herd immunity to exert a protective effect upon the entire population is dependent upon infectivity of the circulating strain (National Institute of Allergies and Infectious Diseases, 2010; Fine, Eames, & Heymann, 2011).

To explain this, consider a distant city in which no one is immunized and no one possesses the antibodies to prevent infection. This theoretical city represents the most vulnerable situation where a single individual can potentially become infected and transmit the disease across the entire susceptible population. Viral transmission could be rapid in this city as people live in close proximity to one another, share community services, and use mass transit together. In this simple model, the residents of this city would eventually all become infected with the disease.

However, if a vaccine is introduced to the population, immunized citizens would become less likely to be infected. The vaccine exerts a protective effect by reducing the proportion of susceptible residents in the city. This reduction in each vaccinated resident's susceptibility collectively lowers the probability of an infectious person transmitting and spreading the disease throughout the city population. Decreasing the length of time the infection circulates in the population also reduces the probability of continued viral transmission. As more citizens become vaccinated, the probability of future transmission falls even further, since there are fewer vulnerable people who can be infected. As the proportion of infectious people declines, this further lowers the chances of transmission.

Herd immunity can be an appropriate method in protecting those who are unable to receive a vaccination. For instance, a newborn child who does not have a fully developed immune system response to benefit from the influenza vaccine can be still protected against influenza if the parents and all other family members have been immunized. By protecting themselves, the family members have reduced the chances of being infected themselves and in turn, reduce the chances of influenza entering their household and infecting the newborn child. This family example can be extended to entire populations within geographical areas such as towns, cities, provinces, or regions in real life cases. Herd immunity has been studied in Canada by Loeb et al. In this pivotal paper, Loeb et al. examined secluded Hutterite communities in central Alberta and tested if influenza rates would differ between different communities—those which were vaccinated and those which were not (Loeb et al., 2010). These rural, distant communities were segregated enough from large cities to act as independent populations that were well suited to illustrate any effects of herd immunity. Communities were assigned as a controls or intervention communities. Healthy children were randomly assigned influenza vaccine or control vaccine according to community and laboratory-confirmed cases of influenza were recorded. Loeb et al. discovered that the intervention communities in which healthy children received influenza vaccine had lower case rates overall and that this benefit extended even to those who were not vaccinated. The study illustrated that herd immunity was a significant factor in preventing infection not only in the vaccinated children, but also in the community (inclusive of adults and seniors) as a whole.

Although these results appear to present herd immunity benefits to a population, these advantages were demonstrated in an isolated rural population. Herd immunity in remote isolated communities may not be the same in large metropolitan cities where considerable mixing of

citizens from other locales occurs. The combination of a dynamic population and continuous mixing through mass transportation and air travel potentially questions the extent to which the findings are broadly generalizable remains unclear.

1.5 Current Canadian Influenza Immunization Environment

There is a divergence of immunization programs among provinces and territories (Sibbald, 2003). Each province has developed and designed its own immunization policy, with some provinces choosing to invest in universal programs while others providing publically funded vaccine through targeted programs. There is currently no definitive answer as to the best strategy for immunizing a population against seasonal influenza. Policies differ from region to region and differ over time.

Could Canada's provinces have such different populations that immunization practices differ as well? Admittedly while there are some regional differences (e.g. Maritime Provinces having a higher proportion of citizens greater than 65 years of age), it is highly unlikely that major demographic and epidemiological differences would justify different provincial policies (Statistics Canada, 2015). Critics of interprovincial immunization program differences believe that the lack of standardization may result in negative health consequences (MacDonald & Embree, 2002). Particularly, with the contagious nature of influenza, a patchwork of immunization policies could reduce optimal immunization coverage and limit any potential gains the country may receive from nationwide herd immunity.

Public health stakeholders have an interest in understanding which policies are more effective in protecting the population against influenza. Given the constraints of health care budgets, investigating cost-effectiveness is a pragmatic and essential research objective. Health Canada, provincial Ministries of Health, public health agencies, and privately managed drug benefit insurers need to have a better understanding of the cost-effectiveness of programs in order to decide on how best to protect Canadians from seasonal influenza in the most cost-effective manner.

1.5.1 Provincial Influenza Immunization Programs

As noted, while national recommendations exist, there is no standardized and enforceable federal policy. Influenza immunization policy is set at the provincial level. In Ontario for instance, all residents six months of age or older are eligible to receive an influenza vaccination through

the publically funded system. Known as the Universal Influenza Immunization Program (UIIP), this program started in 2000 allowing Ontarians to receive flu shots from physicians and public health nurses (Kwong, et al., 2008). In the province's commitment to further expand access to this program, pharmacists were recently added as health care professionals who can administer vaccines in 2012 (Government of Ontario, 2012).

As of February 2015, in Québec, New Brunswick, and British Columbia, only selected groups are covered for influenza vaccinations under the province's publically funded program. People outside of these groups are not covered by provincial funding. They can receive the vaccine with out-of-pocket payment (Ministère de la Santé et des Services sociaux, 2014; BC Centre for Disease Control, 2014).

The decision and design of immunization policies can be based on several factors from logistical feasibility, resource availability, to budget impact, but there appears to be no distinct, transparent criteria to select one type of program over another. One particular paper by Erickson, De Wals, & Farand provide some insight as to the process of how Canadian publically funded immunization programs are constructed (Erickson, De Wals, & Farand, 2005). In this framework, the authors describe a series of key questions for decision makers in designing an immunization program. These questions ranged from the burden of disease, vaccine characteristics, political and legal considerations, equity, and cost-effectiveness.

Regarding cost-effectiveness, the *type* of immunization strategy that the province wishes to fund particularly relevant. More specifically, universal programs often require more resources than targeted programs, it is important to understand the economics of whether a universal program can or should be implemented (Erickson, De Wals, & Farand, 2005).

In Canada, the reasons for the differences between publically funded immunization programs are not clear. Interpretation of clinical evidence, political acceptability, manufacturer contracts, and provincial economic situations all contribute to this Canadian patchwork of programs. This research intends to shed light on these programs through a review of relevant economic evaluations and an understanding of the current provincial policy-making climate.

1.6 Background on Health Economics

Health economics is a field of study which blends traditional economic concepts of costs, efficiency, trade-offs, scarcity, incentives, and behaviour, and applies them to health care systems, interventions, and clinical effectiveness to generate optimal health care decisions. When large scale, taxation-funded, public health decisions are to be made, the importance of health economics rises to the forefront of a decision maker's attention.

This section introduces some of the basic concepts in health economics as it relates to influenza immunization programs.

1.6.1 Overview and Purpose of Economic Evaluations

By definition, economic evaluations analyze both the costs and the health outcomes of the intervention under analysis. For health care evaluations, these interventions could include health technologies like specific medications, hospital protocols, surgical procedures, or health promotion programs. For this thesis, the interventions in focus are influenza immunization programs in different populations.

Full economic evaluations jointly analyse the costs and consequences (i.e. health outcomes) of health interventions among possible alternatives. The choice between an intervention and its comparator is instrumental to an economic evaluation. Described by Drummond, Sculpher, Torrance, O'Brien, and Stoddart as the comparative analysis of alternative courses of action based on their costs and consequences, economic evaluations are designed to determine the incremental difference between health based decisions (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997; Higgins& Green, 2011). When deciding on one intervention over another, it is critical to consider the *incremental* costs and *incremental* outcomes of an intervention versus a comparator. Incremental analysis can be defined as an explicit comparison of one intervention to another. It is this difference in cost or health consequence between two alternatives that is important to an economic evaluation. As such, economic evaluations of health care programs calculate the marginal difference between alternatives and assess the change in values of cost and outcomes, summarizing the trade-off if one intervention is chosen over another. This concept is essential in determining the incremental cost-effectiveness ratio (ICER) used in economic evaluations.

To help improve efficiency in health care spending, payers and governments rely on economic evaluations. In addition to the efficiency and cost-effectiveness results from an economic evaluation, policy makers also view decisions in the framework of budget impact analyses (BIAs). BIAs analyse the aggregate cost or direct economic impact of a particular health intervention at the population level and if it is affordable within budget constraints.

It is important to note that efficiency can be delineated into different types, and the WHO provides guidance on the types of efficiency when it comes to economic evaluations of immunization programs. The first type is called “technical” (or “operational”) efficiency. Technical efficiency is the process of making the best choices from a given set of resources to optimize or maximize the effectiveness or efficacy of a program, assuming that a specific program has already been selected. An example of technical efficiency would be making the choice between using larger permanently located clinics or several smaller mobile clinics to distribute vaccines in rural first-nation communities (Initiative for Vaccine Research, 2008). Making the choice between outreach clinics or mobile clinics is under the assumption that providing vaccines for these communities has been selected over other potential health care activities.

Another type of efficiency is “allocative” efficiency, which has broader implications. Allocative efficiency focuses on determining the optimal mix of interventions to maximize health gains within a health care budget (Initiative for Vaccine Research, 2008). This definition of efficiency involves comparisons among differing and diverse potential health care interventions with different outcomes. When faced with limited dollars, provincial health ministries must determine which health programmes to invest in to maximize the health outcomes of the population.
In any efficiency decision, an important related concept is opportunity cost. Opportunity cost is the value of benefits from one intervention forgone when resources are committed to an alternative intervention (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997; Scott, Solomon, & McGowan, 2001). As an example, the opportunity cost of a universal influenza immunization program could be the health care gains that could have resulted if the money had been put towards building new intensive care units in community hospitals (Initiative for Vaccine Research, 2008).

An aspect to consider is the method and design of economic evaluations. Some economic evaluations are conducted alongside a randomized controlled trial (RCT). In this case, costs, resource use, and outcomes data from actual patients are recorded and analyzed together with

the clinical results from an RCT. Another method requires economic modelling in which data, often from several sources (such as a pooled analysis of RCTs) is input into a mathematical model comparing two or more health care interventions. These models are usually designed to address specific localized questions that decision makers may have within a specific setting. Theoretically, an advantage the modeling method versus the alongside RCT method is that by using input data from several sources, models are not limited by only one study's results and are not restricted to short time horizons. On the other hand, as with any model, they are also subject to limiting assumptions that could provide incorrect or inappropriate cost-effectiveness conclusions (Initiative for Vaccine Research, 2008). Thus, regardless of the method, appropriate quality appraisal is crucial for the correct interpretation of economic evaluations.

1.6.2 Analytic Techniques

The results of economic evaluations are influenced by the study design or analytic technique selected (U.S. National Library of Medicine, 2015). There are four types of analytic techniques used in full economic evaluations, summarized in Table 2. Each analytic technique has different characteristics and use. A cost-minimization analysis (CMA) is useful when all significant outcome measures of the alternative choices, such as clinical effectiveness, are considered clinically *equal*. While perfect equality in health outcomes between different activities or interventions is rare in health care, an example could be the comparison between two injectable trivalent influenza vaccines (TIV) such as Fluviral™ or Agriflu™. Both of these vaccines are injectable TIV formulations manufactured by different companies, but are generally considered equally effective in influenza prevention and are used interchangeably among provincial immunization programs. In this case, a CMA could technically be performed where the lowest cost vaccine could be shown to be the dominant choice.

Table 2: Types of Analytic Techniques Used In Economic Evaluations

Analytic Technique	Summary Measure	Incremental Analysis
cost-minimization analysis	$	Difference = $\$program_1$ - $\$program_2$
cost-benefit analyses	$/$ or $ - $	Benefit-Cost Ratio = ($PV_{\$benefit}/PV_{\$cost}$) or Benefit-Cost = $PV_{\$benefit} - PV_{\$cost}$ Where PV = $\sum_{t=0}^{n} \frac{(\text{benefit or cost})_t}{(1+r)^t}$
cost-effectiveness analysis	$/natural unit	ICER = $\frac{(\$cost_1 - \$cost_2)}{(\text{natural unit}_1 - \text{natural unit}_2)}$
cost-utility analysis	$/QALY	$\frac{(\$cost_1 - \$cost_2)}{(Utiles_1 - Utiles_2)}$ Usually written as: $\frac{(\$cost_1 - \$cost_2)}{(QALYs_1 - QALYs_2)}$

PV = present value
ICER = incremental cost effectiveness ratio
QALY = quality adjusted life year

In a cost-benefit analysis (CBA), costs and health outcomes are monetized, time adjusted into present value dollars, and the difference between the costs and the benefits are calculated. An advantage to the CBA is the conceptual simplicity in dealing with only monetary units. However in practice, appropriate monetary valuation of health care outcomes is complex, and as such, subjective judgments need to be made on the dollar value of health outcomes. Several techniques are used to accomplish this task. Valuation of health outcomes into a dollar value can be performed by willingness-to-pay surveys where various participants, from patients and family members to health care providers and payers, are surveyed about how much they would

be willing to pay in dollars to achieve a certain health outcome. These results are then used in the valuation and calculations of the CBA. With the provision that these techniques are valid and that the outcomes can be measured and valued accurately, a CBA may be useful in judging a program's net monetary worth over another.

While a CBA relies on the monetization of health outcomes, another commonly used analytic technique is the cost-effectiveness analysis (CEA). A CEA compares alternatives keeping costs in dollars but outcome measures in natural units. Which natural units are used depends on the disease, treatment, and clinical measures typically used in practice since natural units differ according to the type of health intervention being evaluated. For instance, natural units could be life years, blood pressure, lipid levels, psychiatric scale measurements, or cases of influenza. So while costs remain as dollars, the ratio calculated from a CEA is presented as incremental dollars per natural unit gained, averted, or lost. Decision-makers can see how many additional dollars it would cost to achieve an additional natural unit. CEAs are suited for comparing a group of interventions that affect the same natural unit.

However, CEAs often can be troublesome in that there are no set or standard cost-effectiveness thresholds to help decision makers determine if an intervention is cost-effective or not. How much is an additional natural unit worth? Additionally, it is difficult to value interventions across different natural units or in diverse disease states and conditions. Among differing natural units, CEAs do not present a clear choice as to which one provides the most value for money. To make a comparison among differing health care programs, there needs to a common point of reference or denominator which a cost-utility analysis (CUA) provides.

To start, the definition of utility is essential for understanding the CUA. Utility is a preference-based quality of life measure defining the favorability or desirability an individual has for one health state compared to other health states. To illustrate this concept, if on a scale anchored by 0 to 1, where perfect health is framed as a utility score of 1, and death a utility score of 0, various health states fall between 1 and 0. A more severe illness may have a utility score of 0.2, while a minor illness would be rated as 0.8. Less preferred health states have lower utility measures. There are even some situations where death is given a higher preference than certain health states which are assigned negative utility scores (Woo, et al., 2012).

The calculation of these utility scores requires the use of several research techniques to determine which health states are more favoured or desired than others. Methods to measure utility include the visual analogue scale (VAS) or the standard gamble. The VAS is a systematic scale which derives a preference score by asking participants to rank order or mark on a visual plane which health outcomes are more favoured compared to another. This could simply be marking on a linear scale of 0 to 100, where the low anchor of 0 is death and the high anchor of 100 is perfect health. A more complex method, the standard gamble, asks a respondent to make a discrete choice between remaining in a chronic health state or taking an experimental treatment (the "gamble") (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997). The gamble can result in either recovering to perfect health or leading to instantaneous death. The researcher indicates the probability of death in taking the gamble, and the respondent then chooses whether to stay in the chronic health state with certainty, or take the "gamble". By varying the probabilities of instantaneous death, one can determine the utility value of the chronic health state by determining when the respondent is indifferent between the two choices. In the case that the indifference point is at a high probability of instantaneous death, this indicates that the utility of the chronic health state is low.

Utility scores are used typically to determine quality adjusted life years (QALYs) for CUAs. The scores are multiplied by units of time that the person spends in that health state to calculate QALYs. A year lived in perfect health would result in a QALY of 1 (utility score of 1 multiplied by one year). In contrast, a year lived in illness with a utility score of 0.5 would result in a QALY of 0.5 (utility score of 0.5 multiplied by one year). In this example, these QALYs imply that a year lived with this illness is comparable to living only 6 months in perfect health. Essentially, QALYs measure the time lived in certain health states to describe both morbidity and mortality in a single measure.

QALYs, as well as other measures such as disability adjusted life years (DALYs) are used across various health care interventions so diverse health interventions can be compared through a CUA (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997). DALYs are a combination of the life years lost due to mortality and morbidity of a disease and are a standardized measure of disease burden. QALYs are similar but are a measure of health, with similar combination of life years (mortality) and morbidity of a disease. QALYs are thought of as a measure of health gained, while DALYs are a measure of burden averted.

ICERs in CUAs compare the difference in costs and health outcomes between the two alternatives representing the additional cost per additional QALY between the intervention and comparator. These ICER calculations include the incremental costs of the interventions compared in the numerator of the calculation and the incremental QALYs of the interventions compared in the denominator of the calculation. CUAs can demonstrate the relative value across different alternatives with different natural units and can be used to assess allocative efficiency (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997; Public Health Agency of Canada, 2002; Initiative for Vaccine Research, 2008).

Using CUAs, decision makers can compare diverse alternatives. A health intervention that is less costly and more effective in generating QALYs (or averting DALYs) is the dominant choice versus comparators, and interventions that are less effective in generating QALYs and more costly are dominated and are eliminated from the consideration set. But what if an intervention was both more effective in generating QALYs and more costly? In this case, is the incremental cost worth the incremental effectiveness? This is when additional context and interpretation is necessary for a decision to be made and often, cost-effectiveness thresholds are used as guidelines of determining the acceptability of an intervention. Generally, in Canada there is no specific threshold, but a range of $20,000 to $100,000 per QALY is used along with the context of a decision maker's priorities and the interventions' place in therapy (Laupacis, Feeny, Detsky, & Tugwell, 1992).

Although there may be many definitions and types of economic evaluations in health care, the underlying principle is the comparative and incremental nature of the analysis. Decisions such as selecting a new drug compared to an older one or a surgical procedure compared to intensive drug therapy are done at the margins to see the incremental costs and the incremental outcomes of each alternative.

1.6.3 Parameters within Economic Evaluations

Similar to RCTs which measure the clinical efficacy of a treatment versus a control, economic evaluations determine the cost-effectiveness of an intervention versus a comparator. However, the difficulty with economic evaluations is that they are often conducted with a set of localized input parameters which likely vary from jurisdiction to jurisdiction. For instance, the cost of health services, such as the salary of nurses, may be different from one province to another.

Generally economic evaluations are designed to describe a localized situation, but there are various methods such that the cost-effectiveness results, like the results of clinical efficacy trials, could be synthesized, summarized, and made more broadly applicable—this will be discussed in a later section.

There are several elements or parameters economic evaluations are comprised of. A non-exhaustive list of these elements includes:

1. Perspective
2. Time Horizon
3. Costing
4. Setting
5. Discounting
6. Variability and Uncertainty

For the purposes of this introduction, the following section will describe these six elements. There are other important elements of an economic evaluation such as population, health outcomes, and intervention/comparators.

1.6.4 Perspective

The perspective of an economic evaluation is critical as it determines the viewpoint for costing and the range of impact and social entities included in the interpretation of the results. A change in perspective can greatly affect the results and interpretation of the study. This key parameter determines the relevance and use of an evaluation and should ideally fit the needs of the target audience (Canadian Agency for Drugs and Technologies in Health, 2006).

The perspective can be narrow, from a specific hospital or single private insurer, to wide, such as the entire public healthcare system or a full societal view. Depending on the perspective, specific health resources and associated costs are included in or excluded from an evaluation. For instance, a societal perspective includes all costs, from a patient's losses in productivity due to workplace absences, to the health care system's costs by way of physician salaries, to direct medical and treatment costs of medication acquisition. On the other hand, a narrower health care system perspective would only include costs that the health care system pays for. It would disregard any costs paid for by the patient and productivity losses which society would end up paying for.

An important note on definitions of perspective is with regards to “health care system” and “third party” perspectives. These definitions can often vary depending on the location since health care systems can differ across countries or even within countries. Clarity on the definition helps to provide a better understanding of the results. For instance, the health care system in the United Kingdom and Canada are highly encompassing, paying for the majority of physician visits, hospitalization costs, and in some cases, outpatient services and drugs. However, in the United States, for a majority of the population, private or third party insurers pay for most of the health costs instead of a single governmental system. In the Methods section a specific definition will be used throughout this thesis where “health care system” will refer to the publically funded systems and “third party” will refer to private insurers. As a reference, Table 3 shows the costs that are included in each perspective with examples for an immunization program (Canadian Agency for Drugs and Technologies in Health, 2006).

Table 3: Perspectives of Economic Evaluations and Related Costs

Perspective		Types of Cost	Examples
Societal	**Public Health care system**	Direct costs to publicly funded health care system	• Vaccine acquisition cost • Cold chain and storage costs • Equipment, space, facilities, and associated overhead • Physician and nurse time • Hospital services, visits, ambulance services • Disposal costs • Immunization awareness campaign costs
	Patients, Families, Employers, School Systems	Direct costs to patients and their families	• Out-of-pocket payments (co-payments and physician/nurse charges) • Cost of travel for treatment and caregivers
		Productivity costs to patients and their families	• Patient’s time spent for travel and receiving treatment • Lost time at unpaid work (e.g. housework) by patient, or parents in the case of children • Lost school days
		Productivity costs to employers and schools	• Lost productivity due to reduced working capacity • Work absenteeism, both short-term or long-term • Costs to employer to hire and train replacement worker • Lost classes/education for children absent from school • Additional teaching/lesson time for children

Adapted from Guidelines for the Economic Evaluation of Health Technologies, Canadian Agency for Drugs and Technologies in Health, 2006.

1.6.5 Time Horizon

The time horizon of an economic evaluation refers to the length of time that costs and outcomes are captured throughout the analysis. Depending upon the time horizon, relevant costs and outcomes will differ. In the case of influenza infection for example, the time horizon should be long enough to capture the respiratory illnesses associated with the infection as well as any longer term complications and hospitalizations that may occur during a flu season. A time horizon set to a single flu season may be sufficient, but may run the risk of not capturing events occurring later, such as long term sequelae following acute illness. Ideally the time horizon should capture all of the material costs and outcomes of both intervention and comparator. In practice however, it is unnecessary to extend the time horizon beyond the period where there are no material costs or relevant outcomes (Canadian Agency for Drugs and Technologies in Health, 2006).

1.6.6 Valuation of Costs

Health care resources such as vaccines administered or physician visits are used to improve health outcomes. Costs are valued by multiplying the quantity of units consumed by the unit price. The estimation of the dollar value for each resource is important to an economic evaluation. These estimations of value need to be made transparently, as it is possible that economic evaluations with similar research objectives and designs could have significant valuation variations.

The valuation of costs is generally determined through aggregate costing or unit costing (micro-costing). Aggregate costing, typically simpler and faster than micro-costing, is to estimate the overall cost of a consumed resource. Micro-costing instead provides more explicit details at the unit level of each resource valued. In either case, both of these strategies ultimately depend on the availability and accuracy of the sources being used. The source, place, and year of data for resource quantities and unit prices, and rates used for inflation and currency conversion need to be valid and clearly stated. An imperfect valuation, whether though imprecise sources or rough estimations, can impact the results of an economic evaluation; to help with this fact, a well conducted sensitivity analysis can test the effect of ranges of cost estimates and provide insight across a range of valuations and inputs (Canadian Agency for Drugs and Technologies in Health, 2006). This will be discussed in a later section.

In summary, cost valuations can vary significantly because there are several approaches that can be used to estimate costs. These approaches are based on available data, required or desired level of precision, and the effort, time, and resources available in performing the economic evaluation. With influenza vaccines, it is quite common to have different cost estimates for the vaccine itself because the vaccine price could be stated differently depending on the context of the purchase. Governmental vaccine purchases typically are large in volume and often access special pricing or delivery and shipping terms from the manufacturer. These terms are often confidential, contractually binding, and are not revealed to the public. What is often available to the public is the market price of the vaccine, but it may not account for the actual price the decision makers may be negotiating with manufacturers, wholesalers, and other suppliers.

1.6.7 Jurisdiction and Setting of Care Delivery

Each country, province, region, city, or hospital has distinct local differences in their respective economic environments, standard of care, and health systems and so it is important that the jurisdiction of the economic evaluation is taken into account. The jurisdiction of each economic evaluation influences the interpretation considerably and alters the generalizability of the study results (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997). Ideally, the jurisdiction used in an economic evaluation is applicable and realistic to the decision maker's local jurisdiction so that transferability of the results is possible.

Setting of care delivery may also differ by healthcare structures and environments. For instance, a vaccination based on primary care physician administration in an exam room would be different than a public mass vaccination clinic in a local community centre. Mass vaccination clinics with scale economies are designed for higher volumes of patients and often are more economically attractive than primary care administration.

1.6.8 Discounting

The value of a resource differs over time—this is a concept central to modern finance and is referred to as the time value of money (Berk, DeMarzo, & Stangeland, 2013). The time value of money dictates that costs and gains realized at different times need to be valued differently. Similarly, costs and health outcomes in health care economic evaluations follow the same principle. There is a societal preference for resources, money, and health benefits to be realized today rather than tomorrow. This positive time preference puts a higher relative value on money,

resources, or health benefits in the present or near future than in the distant future, and so an adjustment needs to be made when calculating costs and health outcomes that occur at different times. This adjustment is achieved by 'discounting' (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997). A health outcome that occurs ten years later is valued less than that same health benefit today. Thus the value of that future health benefit needs to be reduced or discounted by a certain amount. This amount is the discount rate and is applied to money, resources, and outcomes that occur at a future point in time. Costs that occur in the distant future are discounted more (i.e. worth less) than those occurring in the present or near future. Because of this, discounting can have a significant impact on the results of an economic evaluation, particularly those with long time horizons.

For historical and pragmatic reasons, analysts have been using a discount rate of 5% per year throughout the late 1970s and 1980s in publications in the *New England Journal of Medicine* and as a result 5% per year has become the *de facto* discounting rate (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997). In Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) issued guidelines regarding economic evaluations and recommends the use of 5% per year as discount rate (Canadian Agency for Drugs and Technologies in Health, 2006). Since these discount rates apply on a yearly basis, an economic evaluation with a long time horizon of several years will be more impacted by discounting than an evaluation with a shorter time horizon. Alternate discount rates that could be used include the social discount rate, the public or private sector discount rate, and the rate of matching length treasury bonds. In any case, a range of discount rates can be used in an evaluation, from 0% (no discounting) to 5% per year or higher to test the robustness of the results. Sensitivity analyses, discussed in the next section, can provide insight as to how certain variables, such as discount rate, can affect results.

1.6.9 Variability and Uncertainty

With the exception of economic evaluations done alongside RCTs, model-based economic evaluations rely on inputted data. Because uncertainty exists in virtually all of the inputs of an economic analysis, a sensitivity analysis should be performed. A sensitivity analysis examines whether the results of an economic evaluation would change if inputs were to vary under alternative scenarios and assumptions. By testing ranges of inputs such as vaccine effectiveness, rate of infection, health care resource use, discount rate, or vaccine prices, one can see the impact on the results.

The main techniques of sensitivity analysis that are commonly practiced are:

- Univariate or one-way sensitivity analysis
- Multivariate sensitivity analysis or scenario analysis
- Extreme case (best and worst case scenario) analysis
- Probabilistic sensitivity analysis

Given a range of values for inputs, all of these techniques can test the robustness of results, assumptions, and analytic approaches, and aid in interpreting results with missing or censored data. In a univariate or one-way analysis only one input parameter is varied at a time. In multivariate analysis, several parameters are changed simultaneously. Appropriate sensitivity analysis can provide insight if results dramatically change under different scenarios. Scenario analysis incorporates making different assumptions and defining different scenarios and then observing the results—often the testing involves the extremes. Best-case worst-case scenarios for instance, try to simulate the limits of the evaluation to show decision makers the most extreme results that could occur.

Finally, probabilistic sensitivity analysis (PSA) involves the use of simulation methods to randomly sample the data and repeat a calculation over many iterations to generate an average result often in the form of a characteristic distribution curve. Commonly used in PSA is the Monte Carlo simulation technique, where variable inputs are simultaneously subject to a random sampling (Doubilet, Begg, Weinstein, & Braun, 1985). For each iteration, the results of the model change. As this scenario of random sampling is repeated several thousands of times, a distribution curve of results is created and illustrates the potential range and probability of the model's results.

1.7 Potential Limitations of Systematic Reviews of Economic Evaluations

The systematic review process of economic evaluations, while similar to systematic reviews of clinical safety or efficacy studies also carries with it some unique differences and associated limitations. Economic evaluations exist within a myriad of health care systems, political structures, and service settings, with different costs, resource use estimates, opportunity costs, and subsequent conflicting valuations of interventions and comparator (Anderson, 2010). Distinct policy contexts, budgetary constraints, and individual health system architectures limit and influence the generalizability of a particular study to another setting. Therefore a systematic

review of economic evaluations which attempts to summarize these studies will be inherently subject to the heterogeneity of the included studies' designs, methods, and reporting of results. The complexity and heterogeneity of economic evaluations and associated systematic reviews can be addressed through appropriate synthesis, compatible with the appropriate needs of the decision-maker. Answering the question 'what is the cost-effectiveness of intervention X (compared with Y or Z)?' may assume that all economic evaluations are uniform and relevant to the context at hand and so it is essential to contextualize the results to the specific needs of the decision maker in the associated jurisdiction(Higgins & Green, 2011). An appropriate summary of the available literature can be a helpful tool for decision makers as a reference point for continued study and research, even in varying locations.

While clinical safety or efficacy studies are designed to test hypotheses, the intention of economic evaluations is to inform about *particular* decisions in a *particular* context. For an economic evaluation to inform in decision making, it needs to be both of high quality (internal validity) and relevant (external validity) to the question it is addressing.

When it comes to internal validity, one way to ensure high quality is to perform a formal quality appraisal. A critical appraisal of the quality of economic evaluations ensures that only high quality and relevant data are included in a review. Some well-known and validated appraisal tools for economic evaluations are the British Medical Journal (BMJ) checklist of 36 questions, the 10 question Drummond checklist (British Medical Journal, 1996; Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997), and the Phillips checklist (Phillips, et al., 2004) especially for model based economic evaluations. Additionally, several quality assessment instruments, scales, and measurement tools have been created for certain purposes, such as the Pediatric Quality Assessment Questionnaire (PQAQ), developed by Ungar and Santos for the purposes of appraising the quality of pediatric health economics literature (Ungar & Santos, 2003). The Scottish Intercollegiate Guidelines Network (SIGN) has compiled a list of several different quality assessment tools as well, with a specially designed checklist for economic evaluations (Scottish Intercollegiate Guidelines Network, 2015).

These instruments are often split into several domains or categories like study design (comparators, population, time horizon, etc.), costs and resource use, data collection, and reporting methods. Each instrument differs in its number of questions, wording of questions, and scoring method and possesses its own strengths and limitations. For instance, a shorter quality

assessment instrument may be useful when assessing a large quantity of papers in a shorter amount of time, but may lack the depth and detailed appraisal that lengthier instruments with more questions may be able to provide.

Question design is also an important aspect to consider. Instruments with closed-ended questions are answered with “yes,” “no,” or “not applicable.” Open-ended questions are answered in free form responses which provide flexibility in reviewer responses, but may be more difficult to standardize across studies and reviewers. Numerically based scale questions require the reviewer to propose a numerical score for each question which may allow for simpler averaging and weighting, but could also add methodological complexities such as determining and valuating quality cutoffs and ranges.

Ultimately, a quality appraisal instrument needs to fit the research objective, area of study, and the content of literature included in the review. Low quality economic evaluations do not carry as much importance as those which are high quality, and could even be excluded from a review.

1.7.1 Summarizing and Synthesizing Economic Literature

As a tool for the decision-maker, systematic reviews are by design, intended to screen for relevant primary studies, appraise the literature, and summarize it to inform on the current state of the scientific evidence. The most essential components of the review for a decision maker are the results, findings, and discussion which act as a platform for making an informed decision with best available evidence.

In systematic reviews of clinical efficacy and safety, often an overall effect size can be calculated and derived. This overall effect size shows the direction (whether positive or negative) and magnitude of an effect across all of the included studies. However, systematic reviews of economic evaluations may not be able to generate the same statistical summary due to the diverse nature and heterogeneity of results and so qualitative techniques may need to be employed.

Qualitative summaries could be in the form of a narrative, thematic synthesis, or a summary table of key results. These act as a structured summary and form the basis for discussion of each primary study’s characteristics and findings. While quantitative summaries often involve the use of statistical methods such as meta-analysis, qualitative summaries describe the

literature and uncover insights and themes.One useful method is best-evidence synthesis. Best-evidence synthesis, described in a later section, is a method that can be used to summarize complex data when a traditional meta-analysis is not appropriate or possible, while improving on a standard narrative or thematic synthesis (Slavin, 1995).

1.7.2 Quantitative Synthesis: the Meta-analysis

As a traditional quantitative summary technique, meta-analysis is especially useful in clinical efficacy and safety reviews with similar patient populations, intervention and comparator arms, measure outcomes, and settings. Statistically combining results from these kinds of primary studies is considered appropriate. However, for economic evaluations, meta-analyses might not be appropriate or may be incorrectly employed.

By definition, a meta-analysis pools measured outcomes from multiple primary studies and statistically merges them into a single point estimate of the “overall” effect. A meta-analysis weights studies by study size. Larger studies with greater number of patients (greater n) have a smaller degree of variability or error in their measures while studies with smaller number of patients have larger standard errors and impact the overall effect size less. By statistically pooling studies, meta-analyses essentially average the results of the included studies, theoretically increasing the validity of the results, and providing a summary of findings for decision makers.

1.7.3 When Not to Use Meta-analysis in a Review

While a meta-analysis can combine different results from multiple studies, this assumes that the included studies are sufficiently similar to combine. For example, a meta-analysis of clinical efficacy studies of a particular influenza vaccine with comparable participants but with several different study designs could be used to evaluate the clinical effects of that vaccine overall. In these cases an appropriately constructed meta-analysis can derive meaningful conclusions. But there are situations in which a meta-analysis is not the optimal choice to summarize primary studies, which is the case if studies are extremely heterogeneous. Statistically force-fitting extremely diverse studies is the mathematical equivalent of allegorically mashing together not apples with oranges, but apples with television sets—it does not provide meaningful results and in fact, may potentially produce nonsensical results and may conceal the findings of the individual studies themselves. An example of this could be when primary studies have overly diverse and dissimilar interventions, comparators, or populations, to which even the best

methods of standardization are insufficient in finding common ground. There are statistical calculations that can account for heterogeneity, but there are some cases in which an alternative summary method would simply be more appropriate to use.
This is especially the case with economic evaluations, which typically have significant diversity and differences in their design, analytical technique, resource and cost estimates, outcome measure, setting, and context.

1.7.4 Risks of Meta-analyzing Economic Evaluations

By nature, economic evaluations are diverse and inter-study variance is bound to be present. Estimates of costs and resources used, prices, market dynamics, service delivery, and organizational structures vary from jurisdiction to jurisdiction (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 1997). This varies not only between countries but also within a country or across countries, continents, and regions (Drummond & Pang, 2001; Sculpher et al., 2004), and so with the immunization landscape, it is possible and likely that evaluations in Ontario are different to those in the United States or European Union. Some basic variations from different studies can be converted and standardized if certain conditions are met. For instance, costs from different locales can be converted to a common currency and adjusted for inflation by using index calculations.

While it may be true that meta-analysis is theoretically possible, the question to be asked should not be "could these data be meta-analysed?" but instead the question to be asked is "should these data be meta-analysed?"

According to the Cochrane Handbook, there are currently no agreed upon methods for pooling combined estimates of cost-effectiveness (e.g. incremental cost-effectiveness, cost-utility or cost-benefit ratios), extracted from multiple economic evaluations, using meta-analysis or other quantitative synthesis method (Cochrane Collaboration, 2011). In fact, the practice of conducting a meta-analysis of cost-effectiveness data is quite controversial. Subsequently, experts caution when performing a meta-analysis of resource use or cost data (Cochrane Collaboration, 2011). Practically speaking, unless very specific criteria are set and that the data compiled are of sufficient quality and similarity, it is unlikely that a typical quantitative analysis of diverse contexts will provide meaningful information to decision makers. Given these complexities in summarizing economic evaluations, other methods should be employed.

1.7.5 Alternate Methods of Summarizing Data: Best-evidence Synthesis

A best-evidence synthesis can be used when quantitatively summarizing data is not the appropriate choice (Slavin, 1995). Whether conducting a meta-analysis or a best-evidence synthesis, a well-structured review begins with a well-structured research objective to pursue. Layered onto the research objective is the methodology behind the literature search, study scanning, quality assessment, and data extraction from the available literature. To ensure that the review contains relevant, high quality and externally applicable studies is where taking a best-evidence synthesis approach is optimal.

Best-evidence synthesis incorporates the mechanistic rigour of a systematic meta-analysis with the intelligent elements of a narrative synthesis by adopting transparent and explicit study inclusion/exclusion criteria (Slavin, 1995). Well thought out *a priori* inclusion criteria and transparent quality appraisal allow for the most relevant, high quality and externally meaningful studies to be included in the synthesis. This is especially useful when a meta-analysis is not possible, as with economic evaluations. The best-evidence synthesis provision of *a priori* criteria and a quality appraisal avoids some of the limitations of a typical narrative synthesis which may not be as discriminatory in their inclusion of high quality studies or may have bias in the inclusion of certain studies (Slavin, 1995). Only studies which are determined as “high quality” actually are included, equating to a review of the “best” available evidence available.

Best-evidence synthesis, similar to a typical meta-analysis, extracts data from each study in a systematic manner. Studies are screened to extract outcome data, costs, sample size, and resource use for both comparator and intervention arms. The best-evidence synthesis permits for more detailed description of studies of particular high quality. Studies that were excluded are also mentioned with a description and exclusion rationale for these “just missed” studies. This can provide additional insight that a standard meta-analysis may have missed through strict exclusion (Slavin, 1995). Combining a narrative synthesis, *a priori* inclusion criteria, a transparent quality appraisal, with clear, explicit tabulated summary on the design, populations, and results of several studies makes a best-evidence synthesis approach useful in illustrating the results of multiple studies when they could not have been combined with traditional quantitative methods.

A best-evidence synthesis approach of economic evaluations is selected for this thesis. Using this method, a description of inclusion criteria, quality appraisal, reporting of results and

thematic discussion are summarized in this thesis. Results are in the form of detailed tables summarizing the year of study, interventions and comparators, study design, data sources, jurisdiction and setting, analytic perspective and time horizon. To summarize insights and findings, a thematic discussion brings together details, presents rationale, finds relationships, and provides insight for any uncovered themes regarding the cost-effectiveness of influenza immunization programs.

1.8 Rationale for this Study

As a committee of recognized experts across Canada, NACI reports directly to the Assistant Deputy Minister of Infectious Disease Prevention and Control, and works with the Centre for Immunization and Respiratory Diseases of PHAC. One of its main responsibilities is to provide medical, scientific, and public health advice NACI writes annual statements updating on changes in available influenza vaccines and recommendations for influenza vaccinations. The statement includes recommendations regarding future research with respect to influenza vaccines and immunization programs (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). In particular, NACI indicates that there is a need for additional evidence on burden of illness, cost-effectiveness, and programmatic aspects of influenza immunization programs. These data better inform policy decisions at the provincial or local level with respect to publicly funding influenza vaccine programs such as implementing universal influenza immunization programs (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). Driven by the combination of the health burden from influenza, piecemeal vaccination policies across Canada, and a research need from NACI and provincial policy makers, this thesis intends to provide additional cost-effectiveness insight specific to the Canadian influenza immunization environment. A review will offer a broader understanding of the cost-effectiveness of influenza immunization programs across jurisdictions.

Through a systematic review of the economic literature and appropriate quality appraisal together with a best-evidence summary and synthesis, this thesis examines the cost-effectiveness of influenza immunization programs across different populations. In addition, this thesis also describes and comments on various provincial policies to provide public health officials with practical conclusions to use as rationale to support the establishment or continuation of immunization policies.

1.8.1 Research Objectives

The primary research objective is to systematically review and appraise the quality of published economic evaluations of influenza immunization, describe their scope and diversity, and discuss and determine the cost-effectiveness in specific population subgroups.

The specific questions of the primary research objective are:

1. What are the population subgroup sand study characteristics that have been studied in published economic evaluations?
2. What is the quality of the published economic evaluations?
3. What are the cost-effectiveness results of influenza immunization from high quality economic evaluations?

A secondary research objective is to highlight, compare and contrast the various influenza immunization policies across Canada.

2 METHODS

This chapter includes a description of the methods to retrieve the literature and details on the definitions of inclusion and exclusion criteria, databases searched, and search strategies. For the primary research objective, explanations of the inclusion criteria as well as a flow diagram of the literature search are included. This section concludes with a description of the data extraction and synthesis method.

For the secondary research objective, the methods employed to provide additional localized insight and policy context are briefly described. This includes internet searches conducted to retrieve provincial and federal information. These results yielded inter-provincial differences which are later integrated into the results and discussion section of this thesis.

2.1 Systematic Literature Search

The literature retrieval process began with development of search strategies which were implemented across several electronic databases. All search strategies were designed with the assistance of a librarian scientist. Specific search strategies are listed in Appendix 1.

2.1.1 Database Search Strategies

Various standard databases in the biomedical and health economic field were searched for eligible references. Each database was scanned for studies from the inception of the database to February 5th, 2015.

2.1.2 Databases Searched

The majority of search strategies were developed for the OvidSP user interface through the University of Toronto Gerstein Library Database access. Other databases such as Cumulative Index of Nursing and Allied Health Literature (CinAHL) were designed with a different user interface and required the use of Elton B. Stephens Co Host (EBSCOHost). For each database, MeSH headings were screened and selected after reviewing scope notes. Following this, combinations of MeSH headings plus keywords were used to construct a full search strategy. For databases that were not designed for use with either user interface, a combination of keyword searches and Boolean operators were used to retrieve the most relevant records possible. Such databases include grey literature searches and those outside of the University of Toronto Gerstein Library access. In order to properly retrieve literature from the York Centre for

Reviews and Dissemination database, which includes National Health Service Economic Evaluation Database, Database of Abstracts and Reviews of Effects (DARE), and Heath Technology Assessment Database (HTA), a Hospital for Sick Children (SickKids) Library access was used, as these databases were not readily available through the University of Toronto Gerstein Library. Results of search strategies for each database and grey literature are in Appendix 1.

Table 4 lists the databases and keywords used to develop scoping notes, which were then used for development of detailed search strategies. Keywords were matched to database specific indexing terms in collaboration with a librarian scientist.

Additional manual searches using keywords were performed on the CADTH and Cochrane Review websites. Grey literature, which are data generally not published in journals or housed in electronic databases, needed to be searched separately from the published literature. Thus, a grey literature search was performed using CADTH's Grey Matter Database List. This list includes several different national and international HTA web sites, drug and device regulatory agencies, clinical trial registries, health economics resources, Canadian health prevalence or incidence databases, and drug formulary web sites (Canadian Agency for Drugs and Technologies in Health, 2014). A keyword search was performed on February 5th 2015 for "influenza" using this tool to identify any grey literature. In addition to database searches, reference lists of reviewed studies were manually hand-screened for relevant titles. If any new studies were discovered during a title screening of the references, they were validated against the inclusion criteria and included if appropriate.

Table 4: Databases and Keywords Searched

Database	Keywords	MeSH
MEDLINE	Influenza, immunization, vaccination, health economics, cost-effectiveness, costs and cost analysis, fees and charges	orthomyxoviridae infections/ influenza, human/ orthomyxoviridae/ immunotherapy / immunization / immunization, passive/ immunization schedule/ immunization, secondary/ immunotherapy, active/ vaccination/ mass vaccination/influenza vaccines/ economics/ economics, behavioral/ economics, hospital/ hospital charges / hospital costs/ economics, medical/ fees, medical / economics, nursing/ economics, pharmaceutical/ fees, pharmaceutical/ prescription fees
EMBASE	Influenza, immunization, vaccination, health economics, cost-effectiveness	orthomyxovirus infection/ Influenza virus/ immunization/ active immunization/ immunoprophylaxis/ mass immunization/ vaccination/ preventive health service/influenza vaccination/ influenza vaccine/ health economics/ health care cost
CinAHL	Influenza, immunization, vaccination, health economics, cost-effectiveness	Influenza+ / Influenza A Virus+ / Influenza B Virus /Influenzavirus C / Influenza, Human / Influenza, Seasonal/Orthomyxoviridae+ Influenza / Seasonal Influenza / Pandemic (H1N1) 2009 Influenza+ / Influenza, Human+ / Influenza, Seasonal / Orthomyxoviridae+ / Influenza Vaccine / Immunization Programs / Cost Benefit Analysis / Health Care Costs+ / Costs and Cost Analysis+ / Health Facility Costs / / Cost Control+ / Cost Savings / Nursing Costs / Economics, Pharmaceutical Product Evaluation / Program Evaluation / Fees and Charges / Health Facility Charges / Community Health Workers / Community Health Services+ / Community Health Nursing+ / Health Resource Utilization / Health Services Needs and Demand+
NHS EED Centre for Reviews and Dissemination	Influenza, immunization, vaccination, health economics, cost-effectiveness	orthomyxoviridae/ orthomyxoviridae infections/ influenza, human
DARE (Database of Abstracts of Reviews of Effects)	Influenza, immunization, vaccination, health economics, cost-effectiveness	orthomyxoviridae/ orthomyxoviridae infections/ influenza, human
HTA Database	Influenza, immunization, vaccination, health economics, cost-effectiveness	orthomyxoviridae/ orthomyxoviridae infections/ influenza, human
MEDLINE = Medical Literature Analysis and Retrieval System Online EMBASE = Excerpta Medica dataBASE CinAHL = Cumulative Index to Nursing and Allied Health Literature NHS EED = National Health Service Economic Evaluation Database DARE = Database of Abstracts of Reviews of Effects HTA = Health Technology Assessment		

2.1.3 Data Collection

After the electronic database search, records were retrieved and imported to EndNote version #6.0.1. Duplicates were initially removed using the EndNote automatic duplicate removal function. To ensure all duplicates were removed, records were also manually screened to identify any remaining duplicates. Any duplicates that were found were removed.
Title screening occurred after all duplicate records were discarded. Each reference title was screened against the inclusion criteria by two reviewers independently (one reviewer being the author of this thesis). Studies with titles regarding anti-virals, diseases other than influenza, vaccines other than seasonal influenza vaccine, or that were otherwise not related to the objective were excluded. If the title of the study was inconclusive as to inclusion or exclusion, the study would be kept for abstract screening.

After title screening, the remaining studies were then screened by their abstract by two independent researchers. Studies with abstracts which identified that the study did not fit the inclusion criteria were excluded. Studies that were borderline inclusion were held until both researchers regrouped and evaluated each borderline study during an in-person meeting. If after discussion, the abstract screening was still inconclusive as to inclusion or exclusion, the researchers would then review the full paper in more detail for better clarity on whether the study would be included or excluded.

Full text PDFs of studies deemed eligible were retrieved using the EndNote automated literature retrieval function, which accessed the University of Toronto Gerstein Library database. The majority of papers were retrieved in this method. If EndNote was unable to locate the article as full text PDF, a manual search was conducted using the University of Toronto Gerstein Library electronic database or Google Scholar. If every attempt to locate a full text was exhausted, an interlibrary loan was requested between the University of Toronto and an associated partner university. Each study was then saved as a PDF and stored on a personal computer. A printed hard copy was also made for each paper. Following this, data extraction and quality appraisal of the studies was conducted by a single reviewer.

2.1.4 Data Extraction and Management

Data were then extracted from each study and summarized into an Excel spreadsheet. The data extraction parameters are shown with descriptions in Table 5.

An important note on perspective found with these included literature is with “health care system” and “third party” perspectives. Since these definitions vary depending on the location, what is designated as a “health care system” or a “third party” perspective could yield significantly different results.

For these included economic evaluations, “health care system” is defined as a governmental health care system such as found in Canada or the United Kingdom. “Third party” is defined as a private insurer which pays for most of the health costs instead of a single governmental system, more commonly used in the United States.

Table 5: Data Extraction Table Used for Included Studies

Author, Year	Lead author and year of publication
Relevant Target Population	Population in study
Perspective	Perspective taken in study (societal, health care system, third party payer) in accounting costs and outcomes
Analytical Technique	Form of economic evaluation used in study (CEA, CUA, CBA)
Country	Geographic location of study
Time Horizon	Length of valuation and discounting of costs and health outcomes
Currency, Costing Year, and Discounting	Currency used to value costs, currency year, rate of discounting
Model Type	Study model (decision model, Markov, alongside RCT)
Intervention Program	Intervention immunization program
Comparator Program	Comparator (standard of care) immunization program
Costs	General costs included in study
Health Outcomes	Main health outcomes used to determine efficacy of immunization program
Difference in Costs	Incremental cost difference between intervention immunization and standard of care immunization (if any)
Difference in Effect	Incremental difference in health effect between intervention immunization and control/comparator (standard of care) immunization
Results(base case point estimate)	Incremental cost effectiveness ratio or net benefit for intervention immunization program and standard of care immunization program using base case
Results (base case point estimate, 2013 CAD)	Incremental cost effectiveness ratio or net benefit for intervention immunization program and standard of care immunization program using base case converted to 2013 CAD

2.1.5 Selection Criteria

Table 6 summarizes the inclusion criteria. These inclusion criteria were designed to keep the literature relevant to the research objectives and within study design parameters. Additionally, exclusion criteria were also developed to keep the selected literature within the scope of the review's objectives.

For example, the geographic location of an economic evaluation was used as a criterion. Since the geographical location of an economic evaluation is important to its applicability to the current review's research objectives, economic evaluations with a healthcare environment similar to Canada's healthcare environment (i.e. developed countries) were included. Economic evaluations of vaccination programs in developing or emerging nations, as listed in the Organization for Economic Coordination and Development developing country list, or countries that have vastly different health care environments are not likely to be relevant to the Canadian system.

Table 6: Inclusion Criteria Used in Literature Search

Comparators	No structured immunization program or no provision of vaccine, or provision of influenza vaccine to high risk groups only. Vaccine could be through community immunization programs, such as mass vaccination clinics or primary care based immunization.
Geographical Location	Developed nations with similar healthcare environments to Canada
Publication Types	Published full economic evaluations including costs and consequences of the provision of an influenza vaccination program versus a comparator. Analytical techniques for the full economic evaluation would include CEAs, CUAs, and CBAs
Publication interval	From database inception to week 1, February 2015

Only full economic evaluations such as CEAs, CUAs, and CBAs were included. These analytical techniques are relevant to the review as they include valuations of incremental differences in costs and health consequences between intervention and comparator. This is necessary for a comparative evaluation between immunization programs. CMAs, which presume equivalence between two alternatives, base comparisons strictly on the difference in costs. Thus, CMAs are not considered applicable because interventions and comparators within influenza immunization programs are not considered therapeutically equivalent.

Exclusion criteria were created to better define the literature base and reduce the number of irrelevant studies in the search process.

Table 7 summarizes the exclusion criteria used in this search. For example, studies pertaining to anti-virals (i.e. amantadine, oseltamivir, zanamivir), vaccines other than influenza vaccine (i.e. MMR, polio), other diseases such as *haemophilus influenza*, or pandemic influenza, were excluded based on relevance. Pandemic influenza requires a series of different emergency policies based on the acuity of the infection and does not occur on a yearly basis. Seasonal influenza on the other hand is a regular annual occurrence and is treated differently with non-emergency type policies. It is because of this difference that pandemic influenza is not included. Studies that were simply head to head comparisons of vaccine compositions or that were based in countries with a vastly different health care landscape and epidemiology from Canada's, such as developing nations, were excluded.

Additionally, previous systematic reviews, poster presentations, protocol papers, and other unpublished papers were excluded.

Table 7: Exclusion Criteria Used in Literature Search

- Studies regarding:
  - anti-virals
  - vaccines other than influenza vaccine
  - comparisons of vaccine compositions (i.e. with or without adjuvant)
  - other diseases, such as *haemophilus influenza*
  - pandemic influenza
- Poster presentations, research abstracts, previous reviews
- Not in English
- Study design out of scope and protocol papers without results

2.1.6 Quality Appraisal

Each study was examined and appraised using the Scottish Intercollegiate Guidelines Network (SIGN) quality appraisal tool for economic evaluations (Scottish Intercollegiate Guidelines Network, 2015). To account for specific vaccine related items, the SIGN tool was supplemented with five additional questions, created and adapted based on guidance from the *WHO Guide for Standardization of Economic Evaluations of Immunization Programmes* (Initiative for Vaccine

Research, 2008). These additional created questions are more specific to immunization programs and complement the SIGN checklist.

The SIGN quality appraisal tool has nine questions. Each question is close-ended and answered with a “yes”, “no”, or “can’t say” option. For some questions, a “not applicable” answer was used.

The tool provides guidance on the internal validity of each study, asking questions regarding the study design, costing, discounting, and sensitivity analysis. While most studies possess some positive characteristics, there are certain key questions which are deemed “essential.” In order to be categorized as a high quality study, questions 4, 5, and 7 must be answered positively, as recommended from the SIGN checklist guidelines (Scottish Intercollegiate Guidelines Network, 2015).

Question 4 asks whether a study measures and values relevant costs appropriately. This information is essential to the validity of an economic evaluation and studies which did not appropriately measure and value relevant costs were not given an acceptable score. Question 5 examines the measure and valuation of the study’s outcomes measures and question 7 identifies whether there were any deficiencies in the study’s sensitivity analysis. Studies which do not have a “yes” answer for questions 4, 5, and 7 are therefore not used as evidence.

Additional WHO questions relevant to vaccine programs were created and adapted to ask about vaccine administration, efficacy definitions, vaccine wastage, and herd immunity.

Using the principles of best-evidence synthesis, only studies that were of sufficient quality were included in the review (Slavin, 1995). Studies that answered “yes” to essential questions and did not have any severe deficiencies were considered “high quality”. Studies that answered “yes” to essential questions but had some minor deficiencies in other sections of the quality appraisal were categorized as “acceptable” and included in the final analysis and synthesis. Studies that had clear issues across essential questions in the quality appraisal were categorized as “unacceptable” and removed and not included in the final synthesis. Screening out these low quality studies prevented bias from being introduced into the final dataset and potentially generating misleading results. Included economic evaluations needed to demonstrate sound

design, appropriate methods and data collection, and balanced, comprehensive analyses and interpretation.

2.1.7 Literature Synthesis

As stated in previous sections, because of the heterogeneous nature of economic evaluations, a best-evidence synthesis and qualitative approach was used to summarize findings and identify common themes and conclusions. Costs and relevant health outcomes were not quantitatively pooled (i.e. no meta-analysis was conducted) as outcomes were not comparable across economic evaluations that used different designs, interventions, settings, perspectives and had different objectives. Results were grouped by relevant patient populations of interest and thematic commonalities and differences were summarized.

2.1.8 Currency and Inflation

Since economic evaluations varied in currency and year, costs and associated valuations were standardized in the final data summary tables. Monetary results were adjusted to the January 1st, 2013 Canadian Dollar using the Consumer Price Index reported for health care at Statistics Canada (Statistics Canada, 2015) and tabulated. Similarly, foreign currency was standardized. All currency conversion was conducted using the historical currency converter from the OANDA website (OANDA).

2.2 Policy Document Search

For the secondary research objective, localized insight and policy context was summarized in this thesis. Provincial policies were compared through an investigation of provincial governmental health websites as well as from federal governing and advisory bodies. The websites searched were:

- Individual provincial ministry websites
- Health Canada website
- Public Health Agency of Canada website
- National Advisory Committee on Immunization website

Internet website searches were performed to find relevant policy documents. All provincial websites were located with the keywords “influenza immunization” and name of province using Google Search. A list of the provincial, federal and national websites as of June 2015 is provided in Appendix 2.

Inside provincial ministry websites, the keyword search function was used with the search term “influenza”. Provincial programs were categorized as either “universal” or “targeted” and any specific details about the programs were collected using an extraction tool shown in Figure 1. Each province’s website contained specific information regarding their influenza immunization program stating inclusion of various patient groups under the publically funded immunization program. Each website was explored and investigated to find specific policy details and for related documents and web pages. Specifically, the provincial websites were scanned to determine the details of the immunization policy such as which high-risk sub-groups would be provided vaccine within targeted programs.

Figure 1: Extraction Tool Used for Screening Provincial Websites

	Universal	Targeted	Immunization Program Policy Details
BC	“X” if universal	“X” if targeted	Details of provincial policy are extracted and recorded
AB			
SK			
MB			
ON			
QC			
NS			
NB			
PE			
NL			
YT			
NT			
NU			

3 RESULTS

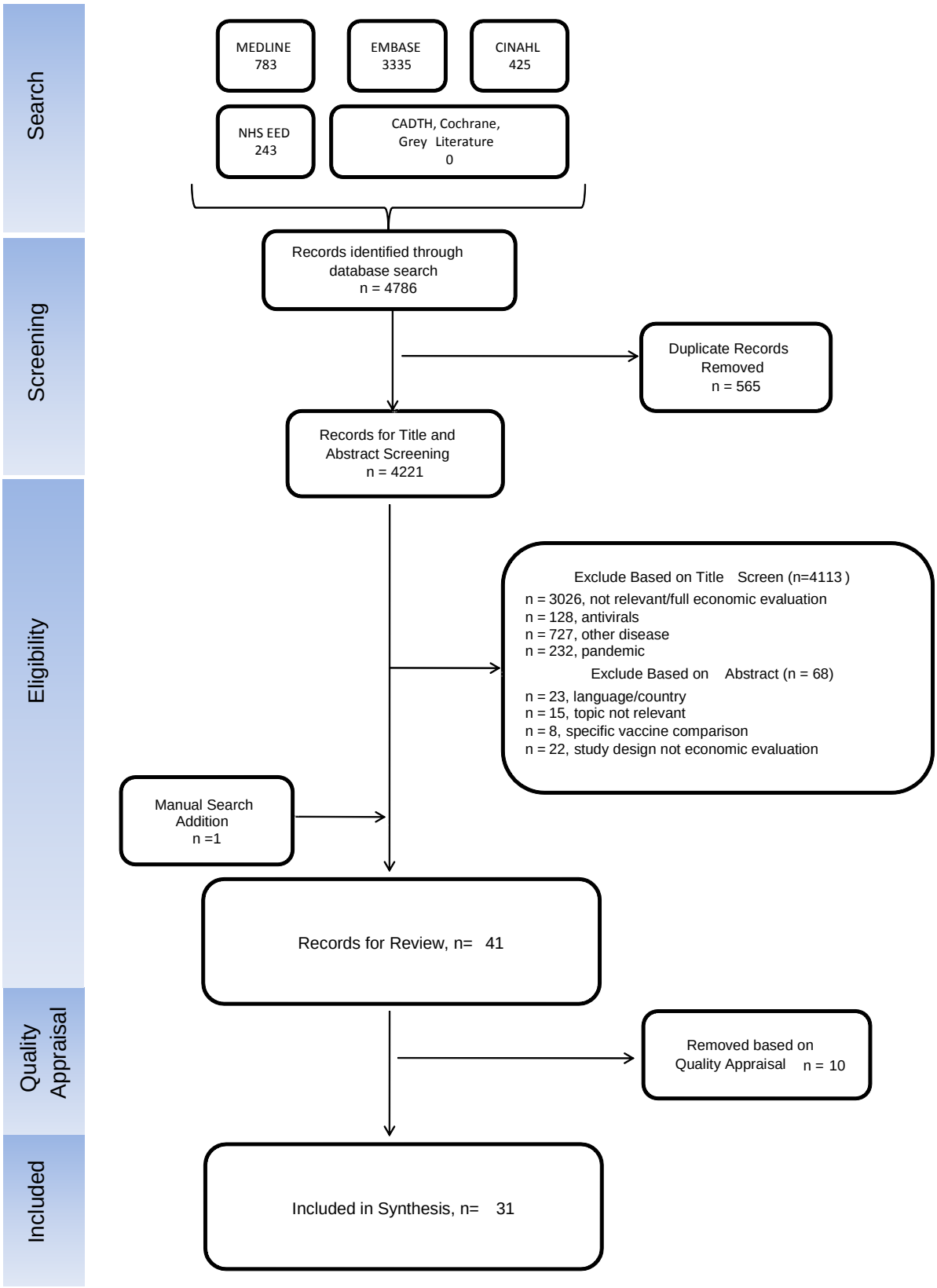
In this chapter, results from the literature search, flow diagram, and quality appraisal are reported. The included economic evaluations are stratified and summarized by population and perspective. A summary of the provincial policy scan results follow.

3.1 Search Results

Using the search strategy, 4786 studies were identified, shown in Figure 2. Of these studies, 565 duplicates were removed, leaving 4221 non-duplicate studies for title screening. Using specified criteria, 4113 studies were removed based on title screening and 68 studies were then removed based on additional abstract screening as these were either generally not relevant, not an economic evaluation, based on another disease, about pandemic influenza, about another vaccine (not influenza), about anti-viral treatment, or did not meet other inclusion criteria. After review of the studies, one study was added by manual hand search, bringing the total number of relevant studies for this review to 41.

The year of publication for the 41 studies ranged from 1996 to 2014. The analytical technique used most frequently among these economic evaluations was the CBA which comprised 20 of the included evaluations. CUAs were used in 19 of the studies and CEAs were performed in two studies. All studies took a societal, health care system, individual, or third party payer perspective with some studies adopting multiple perspectives. Twenty-six of the economic evaluations used a decision analysis model, six used mathematical equations to calculate cost-effectiveness, and seven studies were conducted alongside clinical trials (RCT or non-RCT).One study used a combination of both a decision analysis model and a Markov model (Marchetti, Kühnel, Colombo, Esposito, & Principi, 2007) and one study used a dynamic transmission model (Pitman, Nagy, & Sculpher, 2013).

Figure 2: Flow Diagram of Study Selection Process



3.2 Results of Quality Appraisal

A thorough quality appraisal of these 41 studies was conducted. The appraisal used the SIGN checklist (Scottish Intercollegiate Guidelines Network, 2015) to measure scientific admissibility and a set of created and adapted questions based on the *WHO Guide for Standardization of Economic Evaluations of Immunization Programmes* (Initiative for Vaccine Research, 2008). This second checklist was used to incorporate vaccine specific quality terms and supplement the SIGN checklist. Table 8 shows the results of the SIGN checklist and Table 9 summarizes the detailed results of the SIGN checklist. Table 10 shows the overall results of the additional vaccine related questions and Table 11 summarizes the detailed results of the additional vaccine related questions. Appendix 3 contains summarized information from the ten studies deemed unacceptable.

Unacceptable studies had deficiencies in costing and valuation, lack of a transparent sensitivity analysis, lack of clarity in incremental reporting, or were not accurately or clearly defining vaccine administration or efficacy. Some unacceptable economic evaluations failed to define the population being studied, the perspective being taken, or the assumptions being used in the analysis. Consequently, these studies were considered scientifically inadmissible and removed from the data synthesis. The next section reviews the studies with regard to the questions in the quality appraisal.

Table 8: Scottish Intercollegiate Guidelines Network Checklist Overall Results

	Yes	No	Can't Say
(1) The study addresses an appropriate and clearly focused question	41	0	0
(2) The economic importance of the question is clear	37	1	3
(3) The choice of study design is justified	5	35	1
(4) All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	30	5	6
(5) The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	29	3	9
(6) If discounting of future costs and outcomes is necessary, it been performed correctly	10	29	2
(7) Assumptions are made explicit and a sensitivity analysis performed	33	4	4
(8) The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes	36	3	2
(9) The results provide information of relevance to policy makers	32	6	3

Table 9: Quality Appraisal Summary Table – SIGN Questions

	Author, year	Quality Rating	(1) The study addresses an appropriate and clearly focused question	(2) The economic importance of the question is clear	(3) The choice of study design is justified	(4) All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	(5) The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	(6) If discounting of future costs and outcomes is necessary, it been performed correctly	(7) Assumptions are made explicit and a sensitivity analysis performed	(8) The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	(9) The results provide information of relevance to policy makers
Healthy Working Adults	**Aballéa 2006 (French)**	Acceptable	y	y	n	y	y	n	y	y	y
	Aballéa 2007 (Int'l)	High quality	y	y	n	y	y	n	y	y	y
	Abelléa 2007 (Spain)	High quality	y	y	n	y	y	n	y	y	y
	Buxton-Bridges 2000	Acceptable	y	y	n	y	y	n	c	y	y
	Lee, 2002	Acceptable	y	y	n	y	c	n	y	y	y
	Maciosek 2006	Acceptable	y	y	n	y	y	n	y	y	n
	Mogasale 2011	Acceptable	y	y	n	y	y	y	y	y	y
	Newall 2008	Acceptable	y	y	n	y	y	y	y	y	y
	Nichol 2001	Acceptable	y	y	y	y	y	y	y	y	y
	Nichol 2003	Acceptable	y	y	y	y	c	n	y	y	y
	Turner 2006	Acceptable	y	y	y	y	y	n	y	y	y
Children & Adolescents	**Cohen G, 2000**	Acceptable	y	y	n	y	y	c	y	y	y
	Esposito 2006	Acceptable	y	y	n	y	y	n	c	y	y
	Luce 2001	Acceptable	y	c	n	y	y	n	y	y	y
	Marchetti 2007	Acceptable	y	y	n	y	y	n	y	y	y
	Navas 2007	Acceptable	y	y	n	y	y	y	y	y	y

y = yes; n = no; c = cannot determine, unclear

Table 9: Quality Appraisal Summary Table – SIGN Questions Continued

	Author, year	Quality Rating	(1) The study addresses an appropriate and clearly focused question	(2) The economic importance of the question is clear	(3) The choice of study design is justified	(4) All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	(5) The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	(6) If discounting of future costs and outcomes is necessary, it been performed correctly	(7) Assumptions are made explicit and a sensitivity analysis performed	(8) The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	(9) The results provide information of relevance to policy makers
Children	**Pitman 2013**	High quality	y	y	y	y	y	n	y	y	y
	Prosser 2006	Acceptable	y	y	n	c	y	n	y	y	y
	Salleras, 2009	High quality	y	y	n	y	c	y	y	y	y
	Salo 2006	Acceptable	y	y	n	c	y	n	c	y	y
	Schimier 2008	Acceptable	y	y	n	n	y	y	y	y	y
High Risk	**Avritscher, 2007**	High quality	y	y	n	y	y	y	y	y	y
	Blommaert 2014	Acceptable	y	y	n	y	y	y	y	y	y
	Nichol 2002	Acceptable	y	y	n	y	y	c	y	y	y
Overall	**Clements 2011**	Acceptable	y	y	y	y	y	y	y	y	y
	Sander 2010	High quality	y	y	n	y	y	y	y	y	y
Pregnant & Post-Partum	**Beigi 2009**	Acceptable	y	y	n	y	y	n	y	y	y
	Ding 2012	Acceptable	y	y	n	y	c	n	y	y	y
	Jit 2010	Acceptable	y	y	n	y	y	n	y	y	y
	Roberts 2006	Acceptable	y	y	n	y	y	n	y	y	y
	Skedgel 2011	High quality	y	y	n	y	y	y	y	y	y

y = yes; n = no; c = cannot determine, unclear

Table 9: Quality Appraisal Summary Table – SIGN Questions Continued

	Author, year	Quality Rating	(1) The study addresses an appropriate and clearly focused question	(2) The economic importance of the question is clear	(3) The choice of study design is justified	(4) All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	(5) The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	(6) If discounting of future costs and outcomes is necessary, it been performed correctly	(7) Assumptions are made explicit and a sensitivity analysis performed	(8) The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	(9) The results provide information of relevance to policy makers
Rejected	**Cicchetti, 2010**	Unacceptable	y	y	n	c	c	n	y	c	y
	Campbell 1997	Unacceptable	y	n	n	n	n	n	n	n	n
	Cohen P, 2003	Unacceptable	y	y	n	y	y	n	y	y	c
	Colombo, 2006	Unacceptable	y	y	n	y	c	n	y	y	y
	Kumpulainen 1997	Unacceptable	y	y	n	n	c	n	n	c	n
	Meltzer 2005	Unacceptable	y	y	n	c	y	n	y	n	c
	Parlevliet, 2002	Unacceptable	y	y	n	c	c	n	y	n	n
	Scott, 1996	Unacceptable	y	y	n	n	n	n	n	y	c
	Teufel, 2008	Unacceptable	y	c	c	n	c	n	c	y	n
	Yoo, 2013	Unacceptable	y	c	n	y	n	n	n	y	n

y = yes; n = no; c = cannot determine, unclear

Table 10: Additional Vaccine Questions Overall Results

	Yes	No	Can't Say
(1) Details of vaccine administration were clearly stated	32	5	4
(2) Was an appropriate definition of vaccine efficacy/effectiveness provided and referenced?	34	6	1
(3) Were vaccine safety and adverse events considered?	24	13	3
(4) Vaccine wastage was considered in the study	4	30	7
(5) Indirect effects such as community or herd immunity are considered in the conclusions	6	26	9

Table 11: Quality Appraisal Summary Table – Vaccine Related Questions

	Author, year	Quality Rating	(1) Details of vaccine administration were clearly stated	(2) Was an appropriate definition of vaccine efficacy/effectiveness provided and referenced?	(3) Were vaccine safety and adverse events considered?	(4) Vaccine wastage was considered in the study	(5) Indirect effects such as community or herd immunity are considered in the conclusions
Healthy Working Adults	**Aballéa 2006 (French)**	Acceptable	y	y	c	n	n
	Aballéa 2007 (Int'l)	High quality	y	y	c	n	n
	Abelléa 2007 (Spain)	High quality	y	y	n	n	n
	Buxton-Bridges 2000	Acceptable	y	y	y	n	n
	Lee, 2002	Acceptable	y	y	n	n	n
	Maciosek 2006	Acceptable	y	y	n	y	y*
	Mogasale 2011	Acceptable	y	y	n	y	n
	Newall 2008	Acceptable	y	y	y	y	n
	Nichol 2001	Acceptable	y	y	y	n	n
	Nichol 2003	Acceptable	y	c	y	n	n
	Turner 2006	Acceptable	y	y	y	n	n
Children & Adolescents	**Cohen G, 2000**	Acceptable	y	y	y	n	n
	Esposito 2006	Acceptable	y	y	y	n	n
	Luce 2001	Acceptable	y	y	y	n	y*
	Marchetti 2007	Acceptable	y	y	y	n	y
	Navas 2007	Acceptable	y	y	y	n	n
	Pitman 2013	High quality	y	y	c	n	y

y = yes; n = no; c = cannot determine, unclear; y* = addressed but not included in analysis

Table 11: Quality Appraisal Summary Table – Vaccine Related Questions, Continued

	Author, year	Quality Rating	(1) Details of vaccine administration were clearly stated	(2) Was an appropriate definition of vaccine efficacy/effectiveness provided and referenced?	(3) Were vaccine safety and adverse events considered?	(4) Vaccine wastage was considered in the study	(5) Indirect effects such as community or herd immunity are considered in the conclusions
Children/Adolescent	**Prosser 2006**	Acceptable	y	n	y	n	y*
	Salleras, 2009	High quality	y	y	y	n	y*
	Salo 2006	Acceptable	y	y	n	n	y*
	Schimier 2008	Acceptable	y	y	y	n	y*
High Risk	**Avritscher, 2007**	High quality	y	y	y	n	n
	Blommaert 2014	Acceptable	y	y	n	n	y*
	Nichol 2002	Acceptable	y	y	n	n	n
Overall	**Clements 2011**	Acceptable	y	y	y	n	y
	Sander 2010	High quality	y	y	y	n	y
Pregnant & Post-Partum	**Beigi 2009**	Acceptable	c	y	y	n	y*
	Ding 2012	Acceptable	y	n	y	n	n
	Jit 2010	Acceptable	y	y	y	y	y
	Roberts 2006	Acceptable	y	y	y	n	n
	Skedgel 2011	High quality	y	y	y	n	y

y = yes; n = no; c = cannot determine, unclear; y* = addressed but not included in analysis

Table 11: Quality Appraisal Summary Table – Vaccine Related Questions, Continued

	Author, year	Quality Rating	(1) Details of vaccine administration were clearly stated	(2) Was an appropriate definition of vaccine efficacy/effectiveness provided and referenced?	(3) Were vaccine safety and adverse events considered?	(4) Vaccine wastage was considered in the study	(5) Indirect effects such as community or herd immunity are considered in the conclusions
Rejected	**Cicchetti, 2010**	Unacceptable	n	n	n	n	n
	Campbell 1997	Unacceptable	y	y	y	n	n
	Cohen P, 2003	Unacceptable	y	y	y	c	n
	Colombo, 2006	Unacceptable	y	y	y	c	y*
	Kumpulainen 1997	Unacceptable	n	y	n	n	n
	Meltzer 2005	Unacceptable	n	n	y	n	n
	Parlevliet, 2002	Unacceptable	y	y	n	n	n
	Scott, 1996	Unacceptable	y	n	n	n	n
	Teufel, 2008	Unacceptable	y	y	n	n	n
	Yoo, 2013	Unacceptable	y	n	n	n	n

y = yes; n = no; c = cannot determine, unclear; y* = addressed but not included in analysis

3.2.1 Results of SIGN Questions

The first and second SIGN questions inquire about the appropriateness and focus of the study. Generally, all studies had an appropriately constructed question about influenza immunization and the majority of studies clearly demonstrated the economic importance of the study question. However, moving onto the third SIGN question about the justification of the selected study design, only five of the 41 included economic evaluations stated a justification for the selected study design (Nichol, 2001; Nichol, Mallon, & Mendelman, 2003; Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006; Clements, Chancellor, Nichol, DeLong, & Thompson, 2011; Pitman, Nagy, & Sculpher, 2013). Generally, the selection of one type of study design or model over another was not explicit. For instance, in the majority of the economic evaluations that utilized a decision analysis, there was little to no reasoning of why a decision analysis method was appropriate to the specific study's research objective. Similarly in the Marchetti study, there was no rationale of why a Markov model was selected (Marchetti, Kühnel, Colombo, Esposito, & Principi, 2007). Only the Pitman study described and justified the use of a dynamic transmission model thoroughly (Pitman, Nagy, & Sculpher, 2013).

The first of the essential SIGN questions, Question 4, was with regards to costing and valuation of resource use. Several economic evaluations did not have a transparent method of cost derivation or resource use valuation, and more substantially, some studies did not define a time horizon or a perspective. The lack of a time horizon or perspective impacts included costs, whether discounting was required, and the interpretation of the results. For instance, the Prosser study and Schimier study did not clearly state a perspective taken in the economic evaluation (Prosser, et al., 2006; Schmier, Li, King, Nichol, & Mahadevia, 2008). It was inferable from the economic evaluation and the descriptions in the study that the societal perspective was being used-- and so both studies were included. However, other studies which did not state the perspective were more problematic and difficult to analyze (Kumpulainen & Makela, 1997; Mamma & Spandidos, 2013; Teufel II, Basco Jr., & Simpson, 2008; Wang, Wang, & Chou, 2002; Wang, Lee, Chen, & Chen, 2005). These were unclear with regard to perspective and did not indicate whether appropriate costs were included. One study for instance, did not properly assign costs to the societal perspective, completely omitting productivity costs (Scott & Scott, 1996). As a result, these studies where perspective could not be determined were not included in the analysis.

Another sixteen economic evaluations did not explicitly state a time horizon. The lack of explicitly reporting a time horizon, while not a major detriment to a study, could generate bias in the results if the study author did not use an appropriate time horizon for the analysis. This would leave the reader unaware of the time horizon. For example, if a time horizon was not explicitly reported, it is possible that an overly short time horizon was used in the analysis. This could cause cost valuations of the intervention and comparator to be inaccurate as some health outcomes may materialize in the longer term and may be missed in the analysis. In the case of influenza, failing to report the time horizon can generally be overcome with careful inferences by the reader and as such, these economic evaluations were kept in the final analysis despite this missing piece of information. If perspective and time horizon were missing in addition to other lacking information, then the study was excluded. For instance, the Teufel study failed to clearly define the population of interest in addition to missing the time horizon and perspective and as a result was excluded from analysis (Teufel II, Basco Jr., & Simpson, 2008).

For the next essential SIGN question (Question 5), three of the economic evaluations did not use appropriate health outcome measures relevant to the study question and another nine studies were unclear. Errors in measurement, improper valuations, and inappropriate selection of a valid health outcome reduced the internal validity of these economic evaluations. For instance, in one economic evaluation (Campbell & Rumley, 1997), the main health outcome measure was determined from a group of non-data blinded nurses gathering the frequency of influenza-like symptoms from open-label non-randomized employee questionnaires.

In another economic evaluation (Navas, et al., 2007), the health outcomes were not completely defined, identified, or relevant to the study question. That economic evaluation applied a loose estimate of the incidence of health events related to influenza and extrapolated it to determine the effectiveness of influenza vaccination. This method was not considered to be a robust or well-designed, appropriate measure of the influenza vaccine effectiveness, particularly in light of better measures used in other economic evaluations. Two studies (Colombo, Ferro, Vinci, Zordan, & Serra, 2006; Nichol, Mallon, & Mendelman, 2003) used lost productivity and employee-related costs such as self-reported ILI-related absenteeism, visits to a health care practitioner, and reduced work effectiveness as health outcome measures and as a measure of vaccine efficacy; these values were determined by taking the salaries in their respective countries and multiplying it by the number of days or hours lost due to an infection. The Yoo study did not measure health outcomes in the economic evaluation, instead equating receipt of

vaccine as a measure of effectiveness of influenza vaccination (Yoo, Humiston, Szilagyi, Schaffer, Long, & Kolasa, 2013). Vaccine uptake, while important, is not an appropriate estimate of actual vaccine effectiveness against influenza.

Ten studies explicitly described the discount rate. Twenty-nine economic evaluations did not state or justify the discount rate used in their analysis and two studies were ambiguous. This element of the study's design was not overly detrimental to the economic evaluation because of the nature of influenza infections and their associated health outcomes generally occurring in short time frames; however, it is possible that the health outcomes due to influenza infection could occur in the future and that a longer horizon is necessary. Besides discount rate there were three studies (Colombo, Ferro, Vinci, Zordan, & Serra, 2006; Cohen, Darling, Hampson, Downs, & Tasset-Tisseau, 2003; Clements, Chancellor, Nichol, DeLong, & Thompson, 2011) that did not state the costing year, complicating currency adjustments. For studies that included discounting, the rate ranged from zero to 5% per annum. Discounting was not overly impactful because of the short time horizon generally used in the evaluations, with the exception of the Clements study, Pitman study, and the Sander study (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011; Pitman, Nagy, & Sculpher, 2013; Sander, et al., 2010). Outcomes in these studies included QALYs and lost life years that required a longer time horizon.

With regards to time horizon, variation existed among all of the studies. Time horizon is unique for infectious diseases such as influenza. Most studies were explicit in time horizons of the intervention (vaccination), but since other costs and QALY losses due to premature death occur well beyond the intervention time horizon (i.e. a single flu season), it is useful for analyses to extend beyond the shorter intervention time horizon and accrue these outcomes over an individual's lifetime. With this in mind, three studies (Pitman, Nagy, & Sculpher, 2013; Clements, Chancellor, Nichol, DeLong, & Thompson, 2011; Sander, et al., 2010) explicitly used time horizons long enough to capture costs and effects beyond the time horizon of an initial infection. The Clements study and Sander study accrued costs and outcomes for an individual's lifetime and the Pitman study used a time horizon of 200 years for the population and a lifetime time horizon for each individual. Pitman et al. mentioned that the resulting benefits of a vaccination policy may continue to accrue past shorter time horizons and therefore used a dynamic transmission model with a longer time horizon in the analysis (Pitman, Nagy, & Sculpher, 2013). Other studies were vague about the use of a long time horizon, and in general, the duration of influenza infection was assumed to be relatively short and accordingly, time horizons were kept

short. Most studies used a single year or flu season (approximately 4-6 months) as the time horizon for the intervention.

Four of the 41 studies had problems with sensitivity analyses or model assumptions, appraised in Question 7 and another four studies were vague or unclear. The most common issue with sensitivity analyses was that the evaluation did not properly structure, include, or clearly define the parameters of the analysis. Problems with model assumptions and incremental reporting were also present as discovered through Question 8. Five studies (Campbell & Rumley, 1997; Cicchetti, Ruggeri, Gitto, & Mennini, 2010; Kumpulainen & Makela, 1997; Meltzer, Neuzil, Griffin, & Fukuda, 2005; Parlevliet, de Borgie, Frijstein, & Guchelaar, 2002) did not explicitly state results clearly or incrementally. Incremental results are very important to decision making as it provides a transparent comparisons between alternatives. For example, the Parleviet study did not have an incremental analysis against a standard of care comparator which leaves the economic evaluation incomplete (Parleviet, de Borgie, Frijstein, & Guchelaar, 2002).Of the five studies with problems with incremental reporting, three had fundamental deficiencies with their assumptions that lead to bias. These deficiencies included: no justification of assumptions, using weak or no sources at all, failing to explicitly mention assumption values and ranges, or simply not including an incremental analysis in the study.

As a result of the checklist, Question 9 uncovered that six of the 41 economic evaluations were not providing clear, useful information to policy makers. Often this was due to problems with the design, of important economic evaluation elements (such as sensitivity analysis), or lack of clarity around key definitions. For instance, the Cicchetti study did not define the term “coverage” throughout its evaluation (Cicchetti, Ruggeri, Gitto, & Mennini, 2010) and while this term often refers to number of people vaccinated, it also was being used as a term describing whether payment was reimbursed. The Teufel study did not define the age of children studied (Teufel II, Basco Jr., & Simpson, 2008). Such loose definitions cause potential misinterpretations of the results. Similarly a missing perspective, time horizon, or QALY measure could also be misleading. However, the majority of studies did provide sufficient results and clarity of reporting and an explicit mention of the limitations and assumptions.

3.2.2 Results of Vaccine Related Questions

Five adapted vaccine related checklist questions were used to complement the quality appraisal of the economic evaluations. These questions were not used in the removal of any of the

studies but provided additional information to determine whether a study was considered “high quality” or “acceptable” based on the SIGN checklist.

Nine of the 41 evaluations did not state or were ambiguous about the details of vaccine administration. These studies generally did not provide specifics on where the actual vaccination would take place or did not include details on the time, materials, or personnel required to administer the vaccine to the individual in its costing. These programmatic assumptions may significantly alter the cost and resource use for both intervention and comparator policies and should have been included in the evaluation.

The majority of studies provided an acceptable definition of vaccine efficacy or effectiveness but seven studies did not. These studies were unclear whether laboratory-confirmed influenza (LCI), influenza-like illness (ILI), or another measure of health outcome was used to define vaccine efficacy. In two economic evaluations, vaccine efficacy was simply reported as a general reduction in influenza, without description of what symptoms, definitions, or health outcome measures were being used (Ding, Zangwill, Hay, Allred, & Yeh, 2012; Prosser, et al., 2006). Another two studies were using fairly weak proxy productivity measures such as loss of work days due to influenza like symptoms and visits to a health care practitioner to define vaccine efficacy (Nichol, Mallon, & Mendelman, 2003; Cicchetti, Ruggeri, Gitto, &Mennini, 2010). These measures may be biased and not sufficient given that other stronger definitions or measure of efficacy, such as cases of LCI, could have been used. Others used assumptions that may underestimate or overestimate the real effectiveness of the vaccine, such as assuming vaccination would have an equal reduction across a variety of health outcomes and resources (Meltzer, Neuzil, Griffin, & Fukuda, 2005; Scott & Scott, 1996). And finally, as stated earlier, the Yoo study roughly equated receipt of vaccine (i.e. vaccine update) as an effectiveness measure for their study. Using a series of several assumptions and data from the literature, Yoo et al. calculated that an improved rate of vaccine uptake would translate to a decrease in infection and transmission of influenza from child to household (Yoo, Humiston, Szilagyi, Schaffer, Long, & Kolasa, 2013). This was not considered a reasonable assumption and not of high quality.

Vaccine safety and tolerability was inadequately accounted for or had no mention in16 economic evaluations. These studies did not account for any potential adverse events as a result of the vaccine administration. The other 25 studies captured the adverse effects of the

influenza vaccine in their model inputs or clearly stated an assumption to exclude adverse events.

A common quality gap was the omission of vaccine wastage. Accurate forecasting and purchasing decisions are important for health care systems and this was accounted for in only four of the economic evaluations. An additional quality deficiency was that over half of the studies did not explicitly include any effects due to indirect protection or herd immunity. In total, twenty-six of the 41 economic evaluations did not include any mention of herd immunity, a significant factor in the development of immunization programs. Nine of the economic evaluations addressed the effect of herd immunity in the discussion of results, but did not explicitly include any herd immunity effects in their modeling. Only six of the studies specifically included herd immunity effects in the economic analysis.

3.3 Included Economic Evaluations

Based on the quality appraisal, ten of 41 studies were excluded. The final pool of included studies after quality appraisal totaled 31. From these included studies, five main subgroups emerged: overall population (n=2), healthy children and adolescents (n=10), pregnant and postpartum women (n=5), healthy working age adults (n=11), and those with a high risk of complications such as elderly adults and patients with cancer or other underlying disease, and those with high risk of infection such as health care workers (n=3). These subgroups are important to the development of influenza immunization programs. Pregnant women and elderly adults are typically at a greater risk of experiencing severe respiratory illnesses due to influenza. Similarly, young children are susceptible to increased complications due to an influenza infection (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014). This particular younger age group often is considered more likely to spread influenza infection than other age groups. Healthy working age adults, while often thought of as lower risk of complications have potentially the highest economic impact as productivity losses for employers and society are the greatest with this subgroup. The presentation of results is stratified according to these subgroups.

3.3.1 Pregnant and Postpartum Women

Five studies were specific to pregnant and postpartum women and all were of acceptable quality. Four studies were CUA and one was CBA. The societal, health care system and third party payer perspectives were taken for the economic evaluations. The geographic locations

were the United States, England/Wales, or Canada. For all of the studies, the population examined was pregnant women, except for the Ding study which investigated postpartum women and the subsequent effects of maternal vaccination upon neonate (Ding, Zangwill, Hay, Allred, & Yeh, 2012). These studies were published between 2006 and 2012; Table 12 summarizes the results for pregnant and post-partum women in a cost-effectiveness plane.

Table 12: Cost-effectiveness Summary for Pregnant and Post-partum Women

		Incremental Effectiveness	
		-	**+**
Incremental Costs	**+**		Beigi (Societal) Jit Blommaert Skedgel (no vac & high risk)
	-		Roberts Ding (Societal, TPP)

3.3.1.1 Societal Perspective

The Beigi study, Roberts study, and Ding study performed economic evaluations from the societal perspective in USA (Beigi, Wiringa, Bailey, Assi, & Lee, 2009; Roberts, Hollier, Sheffield, Laibl, & Wendel Jr., 2006; Ding, Zangwill, Hay, Allred, & Yeh, 2012). Beigi et al. and Roberts et al. studied healthy pregnant women, comparing vaccinating all pregnant women to the standard policy of vaccinating high risk pregnant women only. Risk was defined as the risk of influenza infection and respiratory complications and not related to the pregnancy outcome for these studies. Vaccination occurred during a routine prenatal visit. The time horizon for the Roberts study was one year; the Beigi study did not specify a time horizon though it was inferred as approximately one year or a single flu season.

Costs included vaccine acquisition, administration, physician visits, hospitalizations, treatment and drugs, as well as costs related to lost work days or caregiver costs. The actual values used in each study were different. In the Beigi study and Roberts study, the vaccine acquisition cost was similar at $9USD and $10USD respectively but hospitalization costs in the Beigi study was $3,526USD per visit for mothers, $2,323USD per visit for infants (Beigi, Wiringa, Bailey, Assi, & Lee, 2009) and higher in the Roberts study at $5,128USD for pregnant women (Roberts, Hollier,

Sheffield, Laibl, & Wendel Jr., 2006). Physician visit costs in the Roberts study were set at $80.69USD but physician visits were not included in the Beigi study. Deaths were valued in the Beigi study at $5,000USD per death of mother or neonate. The Roberts study assumed deaths would not occur and were not included in the model. Productivity losses in the Roberts study were $49.40USD for an unspecific amount of time, and $16.02USD per hour in the Beigi study.

When looking at the Ding study, unit costs were also generally higher than the Beigi study and Roberts study comparatively. Ding et al. set the vaccine cost higher at $15USD per unit, hospitalization costs per stay at $24,945USD for birth mothers and $14,318USD for infants, and productivity losses at $29.71USD per hour (Ding, Zangwill, Hay, Allred, & Yeh, 2012). Deaths were valued differently in the Ding study compared to the Beigi study. Ding et al. set the value of death of a mother at $100,458USD and of an infant at $37,925USD. Health outcome measures in these three studies differed. Beigi et al. used cases of LCI to determine vaccine efficacy as well as QALYs as a health outcome; Roberts et al. used cases of ILI to define vaccine efficacy and QALYs as a health outcome. The Ding study used an unspecified "rate of influenza," measured as the reduction in the incidence influenza related health resource (outpatient physician visits, hospitalizations) use to determine vaccine efficacy.

All of these studies used a decision-analytic model with inputs from several previously published studies as well as governmental database estimates. The Beigi study and Roberts study both conducted CUAs with data from the United States. Health state preferences (utilities) were taken from database estimates. In the Beigi study, projected life expectancy estimates and utility decrements for pregnant mothers and neonates were determined from the Human Mortality Database (Wilmoth & Shkolnikov, 2008). In the Roberts study, health-related quality of life values for persons with influenza were derived from the Healthcare Cost and Utilization Project. The Quality of Well Being scale was used to estimate the health-related quality of life for persons with ILI and applied to the duration of infection.

The Ding study was stated to be a CBA from the United States, specifically studying postpartum women who had not been immunized throughout their pregnancy and the effect of immunization on neonates. This economic evaluation compared vaccinating postpartum mothers to not vaccinating postpartum mothers. Vaccination occurred in the hospital after birth before the mother was discharged. In this study, the only potential health results for mothers and infants were: infection without medical attention, outpatient treatment (physician visit), hospitalization,

or death. Each of these resultant health outcomes were costed for direct and indirect costs. For instance, if an infant was infected, costs of health resource use would be calculated from the addition of the direct medical costs and indirect costs of treating the infant. Total health care resource costs were estimated from published literature by calculating the unit costs of hospitalizations, physician visits, laboratory tests, consult fees, inpatient and outpatient procedures, and prescription medications, then multiplying by the unit quantity for each study arm (vaccinated or not vaccinated). Productivity losses of the parent were also included by estimating lost wages. Despite being labeled a CBA, there was no attempt to monetize health outcomes such as the willingness-to-pay for avoidance of an infection or a hospitalization. Only costs of health resource use (hospitalizations, physician visits, laboratory tests, consult fees, inpatient and outpatient procedures, and prescription medications) were factored into the analysis. Time off work was valued by using estimating average lost wages in the US. Monetization was only made for deaths by summing the costs of treatment before death plus an estimated indirect societal cost of the death. The treatment costs before death came from a CDC study (Molinari, Ortega-Sanchez, Messonnier, Thompson, Wortley, & Weintraub, 2007) as well as from a Medstat Market scan health insurance claims database which captured data over four influenza seasons. The indirect societal cost per death was estimated by the author, based on a value of statistical life estimates, lost productivity, and the social value placed on a human life estimated from previous literature (Molinari, Ortega-Sanchez, Messonnier, Thompson, Wortley, & Weintraub, 2007).

From the societal perspective, the Beigi study found that the base case scenario of vaccinating pregnant women compared to not vaccinating pregnant women resulted in an incremental cost of $7,718USD per QALY gained in 2004 United States dollars. On the other hand, the Roberts study found that vaccinating all pregnant women compared to only vaccinating high risk pregnant women was a more effective, less costly, dominant strategy. While vaccine efficacy was very similar for both studies at approximately 70% reduction in the probability of an influenza infection in the Roberts study and 73% reduction in the probability of an influenza infection in the Beigi study, the differing results could be due to differences in the value other study inputs, such as the unit cost of the vaccine, and the inclusion of different model inputs. For instance, the Beigi study did not include the costs of mothers going to physicians if infected, instead assuming they would either self-medicate at home or go directly to the hospital; conversely, the cost of physician visits was included in the Roberts study. Efficacy definitions also may have contributed to the difference in results. While the Roberts study used a reduction

in cases of ILI as the measure of vaccine efficacy, the Beigi study used a reduction in cases of LCI. This leads to a different probability of developing an influenza infection. In the Beigi study, using a LCI definition of a case resulted in the probability of influenza infection almost five times lower than in the Roberts study. Using ILI as an efficacy definition can lead to a higher probability of inclusion as influenza infection and can incorporate a lot of cases and symptoms unrelated to influenza infection that could not have been prevented with the vaccine. In this study, no attempt was made to decipher actual influenza cases from symptomatic ILI and an adjustment may have been useful in the analysis. Vaccine effectiveness estimates using ILI may have needed to be adjusted since vaccination technically should not have any material effect on other infections.

The Ding study found that vaccinating postpartum women prior to hospital discharge compared to no vaccination resulted in an average incremental net societal benefit of $12.57USD per postpartum women vaccinated in 2010 United States dollars.

3.3.1.2 Health Care System Perspective

Three studies evaluated influenza vaccination in healthy pregnant women from the health care system perspective. The Jit study was conducted in England and Wales, the Blommaert study in Belgium, and the Skedgel study in Canada (Jit, Cromer, Baguelin, Stowe, Andrews, & Miller, 2010; Blommaert, Bilcke, Vandendijck, Hanquet, Hens, & Beutels, 2014; Skedgel, Langley, MacDonald, Scott, & McNeil, 2011). All studies used a decision analytic model for the CUAs. Data sources for the Jit study were a combination of published literature estimates as well as administrative databases in the United Kingdom, such as population based values from the Office of National Statistics, hospital admissions from the Hospital Episode Statistics database, and primary care consults from the Royal College of General Practitioners Weekly Returns Service database. The data sources for the Skedgel study included published literature and public databases such as the Nova Scotia physician's claims database for physician utilization estimates and the Ontario Case Costing Initiative database for hospital cost estimates. Similarly, the Blommaert study used previous literature, Belgium governmental surveys, and European statistical databases for epidemiological inputs.

The Jit study and Blommaert study both compared vaccinating pregnant women to not vaccinating pregnant women. Indirect protection from vaccination was included in these studies with mothers conferring protection to their infants. The Skedgel study was slightly different in

that two analyses were being evaluated. The first evaluation compared vaccinating high risk pregnant women to not vaccinating any pregnant women. In the second evaluation, vaccinating all pregnant women was compared to vaccinating only high risk pregnant women. Risk in this case was defined as the risk of influenza infection and respiratory complications and not related to the pregnancy outcome.

Vaccination for the Jit, Blommaert, and Skedgel studies was assumed to occur in a primary care environment. The Jit and Blommaert studies assumed the general practitioner administered the vaccine. In addition to the primary care setting, the Skedgel study also included administration in public health clinics. The time horizon for the Jit study was two years as in some scenario analyses, protection lasted for two seasons. In the Skedgel and Blommaert studies time horizon was one year. Health state preferences were taken from estimates from other literature. In determining utilities, the Jit study applied utilities from two previously published studies which utilized EQ-5D questionnaire results and VAS to determine utility weights during an influenza episode (Baguelin, Hoek, Jit, Flasche, White, & Edmunds, 2010; Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006). The Skedgel and Blommaert studies both derived utility weights from the same previously published study (O'Brien, Goeree, Blackhouse, Smieja, & Loeb, 2003). Subsequently, QALY decrements were calculated by using the duration of influenza episodes with these utility weights.

Costs for vaccine acquisition, administration and medical costs such as physician visits and hospitalizations differed among these three studies. The Jit study valued each vaccine unit at £16.37, the Blommaert study at €11.81, and the Skedgel study at $50.38CAD for GP administration and $10.39CAD for administration in a public health clinic. Among these studies, only the Jit study included a measure of vaccine wastage, set to 10% and was applied directly to costs of vaccine acquisition. Hospitalization and GP visit costs also differed. The Jit study used £1,446 per hospitalization and £52 per GP visit, Blommaert applied a value of €1,838 per hospitalization and €63.80 per GP visit, and Skedgel estimated costs at $4,464CAD per hospitalization and $31.81CAD per GP visit.

Additionally, vaccine effectiveness varied across all of the studies as well. In the Jit study, vaccine effectiveness was set to 80% reduction of an infection (unspecified as to ILI or LCI), higher than in the Blommaert study where effectiveness was 59% reduction against LCI and

also in the Skedgel study where there was a 64% reduction of risk of infection (undefined as to LCI or ILI).

From the health care payer perspective, the Jit study found that the base case scenario of vaccinating all pregnant women compared to vaccinating only high risk pregnant women resulted in an incremental cost of £23,000 per QALY in 2008 British pounds. This value included indirect protection passed on from mother to infant. In the Jit study, if influenza protection was extended to two seasons, the incremental cost would lower to £15,000 per QALY gained.
The Blommaert study found that in the base case scenario where no additional physician visit was needed for vaccine administration and indirect protection extending from mother to infant, the result was €6,616 per QALY gained.

Skedgel et al. found that vaccinating high risk pregnant women compared to not vaccinating any pregnant women was both more effective and less costly. This meant that vaccinating high risk pregnant women was considered a dominant strategy with improved health outcomes and lower expenditures. The second analysis, vaccinating all pregnant women compared to only vaccinating high risk pregnant women, resulted in an incremental cost of $39,942CAD per QALY gained in 2010 Canadian dollars. Interestingly, these two results demonstrate that differences in the ICER can be found depending on the intervention and comparator group being considered. In the first situation, it was found that vaccinating high risk pregnant women was dominant compared to not vaccinating pregnant women. The result then changes when the analysis compares vaccinating all pregnant women versus vaccinating only high risk pregnant women. Results between these two analyses differ because the incremental effectiveness for vaccinating all pregnant women compared to vaccinating high risk women is smaller than the incremental effectiveness of vaccinating high risk women compared to not vaccinating pregnant women. On the cost side, the intervention of vaccinating all pregnant women is more costly than a targeted strategy of vaccinating only high risk pregnant women. These factors explain some of the difference in results.

3.3.1.3 Third Party Payer Perspective

Two studies, the Beigi study and the Ding study, evaluated healthy pregnant and postpartum women from the third party payer perspective(defined as a private insurers' perspective), with both studies based in the United States (Beigi, Wiringa, Bailey, Assi, & Lee, 2009; Ding,

Zangwill, Hay, Allred, & Yeh, 2012). In the Beigi study, the third party payer perspective results were not reported in the publication.

From the third party payer's perspective which included direct medical costs but excluded work days lost or other societal costs, Ding et al. found that vaccinating all postpartum women would result in a net societal cost of $13.70USD per postpartum women vaccinated in 2010 United States dollars. This result suggests that vaccinating all postpartum women would not generate net savings compared to no vaccination for third party payers. This result is different than the same evaluation performed from the societal perspective where the result was cost saving (net societal saving of $12.57USD per postpartum women vaccinated). The difference in perspectives leads to different costs being included (or not) in the economic evaluation; in this case for postpartum women, the greatest cost savings are societal costs such as productivity losses and other medical costs not paid for by third party payers.

Table 13 : Data Extraction for Pregnant and Postpartum Women

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Cost Items	Health Outcomes
Ding (Societal), 2012	Healthy post-partum women who have not received vaccination during pregnancy, 18 - 49 years	Societal	CBA	USA	1 year	$USD, 2010, 3%	Decision Model	Maternal vaccination	No maternal vaccination	Vaccine, administration physician visits, hospitalization, treatment/drugs, death, lost work days	Rate of influenza
Beigi (Societal), 2009	Healthy pregnant women, mean age 27.1 years	Societal	CUA	USA	Not reported	$USD, 2009, 3%	Decision Model	Vaccination for all pregnant women	No vaccination	Vaccine treatment/drugs, hospitalization, lost work day	Cases of LCI
Roberts, 2006	Healthy pregnant women, 18 - 44 years	Societal	CUA	USA	1 year	$USD, 2004, no mention	Decision Model	Vaccination for all pregnant women	No vaccination	Vaccine, administration Physician visits, hospitalization, treatment/drugs, caregiving Patient time, travel costs	Cases of ILI
Jit, 2010	Healthy pregnant women, 15- 44 years	Health Care System	CUA	England & Wales	2 years	£, 2008, 3.5%	Decision Model	Vaccination for all pregnant women	Vaccination for high risk pregnant women only	Vaccine, administration, vaccine wastage, physician visits, hospitalization	QALYs
Skedgel (vs. no vaccine), 2011	Healthy pregnant women, age not reported	Health Care System	CUA	Canada	1 year	$CAD, 2010, no need for discounting	Decision Model	Vaccination for high risk pregnant women only	No vaccination	Vaccine, administration physician visits, hospitalization	QALYs
Skedgel (vs. targeted vaccine), 2011	Healthy pregnant women, age not reported	Health Care System	CUA	Canada	1 year	$CAD, 2010, no need for discounting	Decision Model	Vaccination for all pregnant women	Vaccination for high risk mothers only	Vaccine, administration physician visits, hospitalization	QALYs

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; USD = US dollars; CAD= Canadian dollars; TPP = Third Party Payer

Table 13: Data Extraction for Pregnant and Postpartum Women, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Cost Items	Health Outcomes
Blommaert 2014	Healthy pregnant women, 15 - 49 years	Health Care System	CEA	Belgium	1 year	EUR, no mention, no need for discounting	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalizations, deaths	QALYs, life expectancy
Beigi (TPP), 2009	Healthy pregnant women, mean age 27.1 years	Third Party Payer	CUA	USA	Not reported	$USD, 2009, 3%	Decision Model	Vaccination for all pregnant women	No vaccination	Vaccine Treatment/drugs, hospitalization	Cases of LCI
Ding (TPP), 2012	Healthy post-partum women who have not received vaccination during pregnancy, 18 - 49 years	Third Party Payer	CBA	USA	1 year	$USD, 2010, 3%	Decision Model	Maternal vaccination	No maternal vaccination	Vaccine, administration	Rate of influenza

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; USD = US dollars; CAD= Canadian dollars; EUR = Euros; TPP = Third Party Payer

Table 14: Results for Pregnant and Postpartum Women

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Ding (Societal), 2012	$12.57/mother net societal benefit	Not reported	Net benefit of $12.57/mother vaccinated compared to no vaccination	Net benefit of $13.43CAD/mother vaccinated compared to no vaccination
Beigi (Societal), 2009	Not reported	Not reported	$7,718.32/QALY	$9,773.60CAD/QALY
Roberts, 2006	$25.22/mother	-0.00256 HRQL	Dominant. $7,563/QALY if additional prenatal visit with OB/GYN for vaccination	Dominant. $11,386CAD/QALY if additional prenatal visit with OB/GYN for vaccination
Jit, 2010	£1.61M for 570,000 women	3200 (2100-4100) GP consults, 290 (180-420) hospitalizations, 18 (8-30) ICU admissions, 0.33 (0.24-0.42) deaths, 9000 (6600 - 10000) influenza cases prevented, 96 (16 - 180) QALYs saved	£23,000/QALY gained base case, £28,000/QALY without infant protection, £15,000/QALY 2nd season protection	$48,102CAD/QALY base case, $58,559CAD/QALY without infant protection, $31,371CAD/QALY if 2nd season bonus protection
Skedgel (vs. no vaccine), 2011	-$9,485 for cohort of 10000 mothers	0.32 QALYs (0.06 - 0.88)	Dominant	Dominant
Skedgel (vs. targeted vaccine), 2011	$91,143 for cohort of 10000 mothers	2.28 QALYs (0.44 - 6.18)	$39,942/QALY	$40,623CAD/QALY
Blommaert, 2014	€385,978 for 121,363 cohort	3 hospitalizations prevented (26 for neonate), 0.07 death prevented, 58 QALYs for 121, 363 cohort	€6,616/QALY	€9,703/QALY
Beigi (TPP), 2009	Not reported	Not reported	TPP simulations are not shown	TPP simulations are not shown
Ding (TPP), 2012	-$13.70/mother net societal benefit	Not reported	Net benefit of -$13.70/mother vaccinated compared to no vaccination	Net benefit of -$14.64CAD/mother vaccinated compared to no vaccination

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; USD = US dollars; CAD= Canadian dollars; TPP = third party payer perspective; GP = general practitioner; ICU= intensive care unit; HRQL = health-related quality of life

3.3.2 Children and Adolescents

Defining children and adolescents as individuals less than 18 years of age, thirteen studies focused on children and adolescents. Ten were included in the analysis after quality appraisal, with eight studies considered acceptable and two studies considered high quality (Pitman, Nagy, & Sculpher, 2013; Salleras, et al., 2009). Three studies were of low quality and excluded from the review.

In terms of analytic technique, five studies performed a CBA, three studies used a CUA, and one study used a CEA approach. One study (Navas, et al., 2007) used both CEA and CBA. The studies were based in and conducted using data from USA, Italy, England, Wales, Finland, and Spain and examined the effects of influenza vaccination on healthy children and adolescents, with ages ranging from six months to 18 years of age. Many of these studies stratified results by age subgroups such as infants (6 to 24 months), toddlers (2 to 5 years old), young children to adolescents (5 to 11 years old), and teenagers (12 to 18 years).

The evaluations generally compared vaccinating all children to vaccinating high risk children only, or to not vaccinating children at all. Some studies examined programmatic comparators such as vaccination in a flexible or restricted setting (after-hours community clinics) or school and group-based vaccination. The Schimier study for instance examined the economic impact of a school system based influenza immunization program (Schmier, Li, King, Nichol, & Mahadevia, 2008); the Cohen study compared vaccination in a flexible setting, in which vaccination was available outside of work hours, and a restricted setting, in which vaccination was only available during the usual work hours of Monday to Friday, 8:00am – 5:00pm (Cohen & Nettleman, 2000). Included studies took the societal, health care system, and individual/family perspectives. These studies were published between 2000 and 2012.

Table 15 summarizes the results for children and adolescents in a cost-effectiveness plane.

Table 15: Cost-effectiveness Summary for Children and Adolescents

		Incremental Effectiveness	
		-	**+**
Incremental Costs	**+**		Prosser (TIV & LAIV) Marchetti (HCS) Navas (HCS) Pitman (TIV & LAIV) Luce (Societal, individual) Luce (TPP)
	-		Prosser (high risk, 6m – 2y) Marchetti (Societal) Esposito (Societal) Cohen Luce (Societal, group) Salo (Societal & HCS) Navas (Societal) Schimier Salleras

3.3.2.1 Societal Perspective

Eight of ten studies evaluated influenza immunization programs from the societal perspective, with the Salleras study and Pitman study as the exceptions (Pitman, Nagy, & Sculpher, 2013; Salleras, et al., 2009).In their studies, Prosser et al. and Schimier et al. did not clearly define the perspective; however, it was reader inferred that the societal perspective was taken (Prosser, et al., 2006; Schmier, Li, King, Nichol, & Mahadevia, 2008).

Of the studies, the Prosser study had the widest age range, including children as young as 6 months to 17 years of age (Prosser, et al., 2006). Five age subgroups were identified in the study: 6 to 23 months, 2 years, 3 to 4 years, 5 to 11 years, and 12 to 17 years. Each subgroup was then evaluated separately. Similarly, in the Marchetti study of children 6 months to 60 months, a subgroup of toddlers 6 months to 24 months was examined separately (Marchetti, Kühnel, Colombo, Esposito, & Principi, 2007). Most of the other studies did not perform subgroup stratification and studied only a single age group.

Three studies were examining the effects on older children. The Salo study had only a single age group of 6 months to 13 years (Salo, Kilpi, Sintonen, Linna, Peltola, & Heikkinen, 2006), the Schmier study focussed specifically on school children, 5 to 18 years old, and the Navas study

only included healthy children 3 to 14 years old. Younger children were also studied in the Cohen study (6 months to 5 years), Esposito study (2 to 5 years), and Luce study (15 to 71 months).

Generally, administration of vaccine was in primary care offices or local public health units except for the Schmier study (Schmier, Li, King, Nichol, & Mahadevia, 2008), which was evaluating the introduction of a school-based immunization program and the Luce study with a group-based immunization strategy in a school or child-care facility (Luce, et al., 2001).
Time horizons varied for these studies, from as short as a single flu season to as long as five years. Two studies did not report the time horizon used (Salo, Kilpi, Sintonen, Linna, Peltola, & Heikkinen, 2006; Cohen & Nettleman, 2000). Study designs also varied. The Schmier and Luce economic evaluations were alongside clinical trials, and the rest used a decision analysis. Marchetti et al. also utilized Markov modelling.

The Prosser study evaluated vaccination of all children (stratified as high risk or low risk) compared to no vaccination using two different vaccines—trivalent influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV) (Prosser, et al., 2006). Direct medical cost included vaccine acquisition cost, administration, physician visits, over-the-counter remedies, prescription drugs, diagnostic tests, and hospitalizations. Productivity losses of parents and caregivers were accounted for. In addition, the study included costs related to adverse events from the vaccine such as physician visits due to injection site reactions, anaphylaxis, and Guillain-Barré syndrome. In the Prosser study, vaccine efficacy was measured as a reduction in symptomatic influenza; the primary health outcomes measure was QALYs. For TIV, efficacy was assumed to be 69% against symptomatic influenza and for LAIV, efficacy was assumed at 84% against symptomatic influenza. In order to determine utilities, the Prosser study referred to previous literature which utilized time trade off questionnaires. These time-trade-off questionnaires were conducted with adults, asking how much time they would reduce from their own lives to prevent various negative health states in their children; respondents were permitted to trade off more time from their own lives than the actual length of the negative health state if they wished. From these questionnaires, utilities scores were taken and applied to the duration of the influenza episode for children, and QALY losses were determined.

In 2006 United States dollars, the base case scenario comparing vaccinating all children with TIV to not vaccinating children resulted in incremental cost of $12,000USD per QALY gained for

children 6 to 23 months, $18,000USD per QALY gained for children 2 years, $28,000USD per QALY gained for children 3 to 4 years, $79,000USD per QALY gained for children 5 to 11 years, and $119,000USD per QALY gained for children 12 to 17 years. The next scenario was comparing vaccinating high risk children with TIV to not vaccinating resulted in a dominant strategy for children 6 to 23 months and 2 years, $1,000USD per QALY gained for children 3 to 4 years, $7,000USD per QALY gained for children 5 to 11 years, and $10,000USD per QALY gained for children 12 to 17 years. The last scenario comparing vaccinating all children with LAIV to not vaccinating children resulted in incremental costs of $9,000USD per QALY gained for children 6 to 23 months, $15,000USD per QALY gained for children 2 years, $25,000USD per QALY gained for children 3 to 4 years, $72,000USD per QALY gained for children 5 to 11 years, and $109,000USD per QALY gained for children 12 to 17 years. These results demonstrate a correlation between a higher cost per QALY and an older age group. This trend is likely from the greater improvement in health outcomes in younger children compared to older children, with a relatively constant vaccination cost. Even though LAIV was more expensive than TIV ($12.89USD per unit of LAIV compared to $6.86USD per unit of TIV), it was also more effective than TIV which offset the increased cost of LAIV.

Focusing on younger children, the Marchetti, Esposito, Cohen, and Luce studies compared vaccinating all children to only vaccinating high risk children.

In the Marchetti study, children were stratified into two age groups: 6 to 60 months old and 6 to 24 months old. The study included costs for vaccine, administration, physician visits, hospitalizations, and lost work days. Vaccine costs were estimated to be €5.50 per unit, physician visits cost approximately €45 depending on the child, parent, or sibling, and hospitalizations cost €2,050 per visit. Productivity costs were assumed to be approximately €63.50 per day lost. The study also included influenza transmission from the infant to household members, including parents and siblings. Incidence of influenza was set to 16.8% for target children, 8.7% for parents, and 17.6% in siblings. Vaccine effectiveness was set to a 25% reduction in risk of ILI in children 6 to 24 months and 48% reduction in risk of ILI in children 25 to 60 months. Health outcomes in the Marchetti study were cases of ILI and consequently, ILI related events such as acute otitis media (AOM) and lower respiratory tract infections. QALYs lost were determined in this study through adopting utilities that were estimated from the Australian Health Survey and applying them to an assumed one week duration for an influenza episode.

In the Marchetti study, it was found that vaccinating all children aged 6 to 60 months was a dominant strategy, being more effective in reducing cases of ILI at a lower cost. The same dominant result was found for the 6 to 24 month old children subgroup.

A similar age group as the Marchetti study was examined in the Esposito study, which performed a CBA comparing vaccinating healthy children 2 to 5 years old to no vaccination. Administration was in an outpatient setting. These two studies had similar populations of interest, but differed across analytic technique, time horizon, and model inputs of vaccine efficacy and medical costs. As an alongside RCT CBA, the Esposito study calculate direct medical costs which included the total costs of the vaccine and its administration, expenses related to the care of vaccine side-effects, and health care resource use such as hospitalizations, number of antibiotic prescriptions, numbers of antipyretic prescriptions, and physician visits due to ILIs occurring in the study subjects and their households during the study period (Esposito, et al., 2006). There was no monetization of health outcomes and the analysis was performed only on costs of health resource use and lost productivity.

Vaccine costs inclusive of administration were estimated at €73.40 for two doses of vaccine (the amount used in the trial, and typically the standard recommendation for a child 6 months to less than 9 years of age who receives their first lifetime dose of influenza vaccine in that season), physician visits cost €15.24 per GP visit and €20.90 per specialist visit as per estimates from the Italian capitation payment system. Adverse effects were estimated to cost €4.04 per child averaged over the entire age group. Indirect costs in the evaluation included absence from work. Work absences were valued according to the net productivity loss tables per capita from an undefined Banca Italia 2002 report and set to €57.38 for women and €75.04 for men per day lost.

Incidence of influenza during this clinical trial was during a low impact season with less than 15% of the Italian pediatric population reporting ILI. The health outcome used to define vaccine efficacy in the Esposito study was several components of ILI: cases of upper respiratory infection, lower respiratory infection, and febrile respiratory illness. Effectiveness of the vaccine was taken from the clinical trial: 33% reduction in cases of upper respiratory infection, 22% reduction in cases of lower respiratory infection, 26% reduction in cases of febrile respiratory illness, 50% reduction in cases of overall hospitalizations, 32% reduction in cases of antibiotic

use, 29% reduction in antipyretic use, 48% reduction fewer school days missed, and30% reduction in the probability of ILI.

From the Esposito study, vaccinating healthy children 2 to 5 years old in the Italian outpatient setting compared to not vaccinating children was cost saving from the societal perspective of approximately €131.43 per child vaccinated, in 2003 Euros. Despite differences between the Esposito and Marchetti studies, the results are both cost saving and directionally aligned.

A third study on younger children was the Cohen CBA (Cohen & Nettleman, 2000). This evaluation focused on infants and toddlers from 6 months to 5 years of age and compared a flexible timeframe for vaccination (available outside of regular working hours of 8:00am to 5:00pm, Monday to Friday) or a restricted timeframe (only during regular working hours of 8:00am to 5:00pm, Monday to Friday) to not vaccinating children at all. The restricted setting would have a greater impact on productivity as lost work hours would accumulate for parents and caregivers taking time off work for their child's vaccination.

The study included direct costs for vaccine, administration, health resource use costs of treating infected children and adults such as physician visits, treatment drugs, and hospitalizations. Indirect costs included the wages lost by a parent or caregiver who stayed home when a child became too ill to attend day care and the wages lost by parents and caregivers who themselves became infected and missed work. No monetization of health outcomes was performed; only lost productivity from time off work was used in the CBA. Vaccine costs were estimated at $10USD per unit, physician visits at $51USD per visit, antibiotic use at $9.91USD, and hospitalizations at $3,064USD per stay. Adverse effects were assumed to be transient, mild, and without cost. Lost productivity costs were assumed to be $93.40USD for women and $123.40USD for men per day lost.

Incidence of circulating influenza was assumed to be 37%. Health outcomes included in the Cohen study were cases of LCI and other influenza related events such as AOM which were then used to define vaccine effectiveness. Vaccine effectiveness was estimated at 83% in preventing clinically apparent influenza infection and 32% effective in reducing AOM in children less than 5 years old. The results were found to be supportive of implementing a vaccination program as both flexible and restrictive settings were cost saving from the societal perspective.

Both the flexible and restricted timeframe generated savings of $21.28USD and $1.20USD per vaccinated child, respectively.

In a similar study of the programmatic considerations of an influenza immunization program, the Luce study was a CEA conducted alongside a clinical trial that studied infants 15 to 71 months of age (Luce, et al., 2001). Like the Cohen study, this study examined the cost-effectiveness of programmatic scenarios within an immunization program. Two scenarios were compared: individual-based vaccination where a parent or caregiver would have to initiate a visit to a health care facility, or group-based vaccination where the vaccination would occur in a school or child care facility and not cause the parent or caregiver to incur productivity losses. Both scenarios were compared to no vaccination and the ICER result was defined as cost per ILI fever day avoided. The natural unit of ILI fever day avoided was measured from the alongside clinical trial. The vaccine used in this study was LAIV.

The Luce study included direct medical costs associated with vaccination, such as vaccine cost, administration, and personnel. Health resource use costs for physician visits and hospitalizations were included as well. Vaccine costs inclusive of administration were estimated at $20USD per unit, physician visits at $55.25USD per visit, and hospitalizations at $2,108USD per stay. Additionally, phone consultations to a nurse, testing and diagnosing costs, over-the counter drugs, lost productivity, and transportation costs were also included. No adverse effects were present in the alongside clinical trial and therefore not included in the analysis. The study included the indirect effects that an infected child would potentially transmit the influenza virus within the household, assuming a transmission rate of 18% from children to household members. Lost productivity costs were assumed to be $13.15USD per hour of work lost. The health outcome used in the Luce study was ILI fever days, a proxy measure for actual cases of ILI. Vaccine effectiveness was determined directly from the clinical trial findings, with vaccinated children averaging 1.2 fewer ILI fever days than unvaccinated children.

The results from the Luce study suggest that group-based vaccination (i.e. in a school or child care facility) was more effective and less costly while the individual-based scenario had an ICER of $29.67USD per ILI fever day avoided, in 1998 United States dollars.

From this result as well as the Cohen study results, it is clear that reducing the productivity loss of a parent or caregiver has a significant impact on the resultant societal cost. The Cohen study

found that a flexible schedule permits parents and caregivers to have children vaccinated during off-work hours and reduces the productivity losses that a restrictive schedule may generate. The Luce study reinforced that a group-based scenario in a school setting does not require parents or caregivers to take time off work and thus improves the societal cost-effectiveness of the program.

Three studies focused on older children, adolescents, and teenagers. Using a decision model, the Salo study analyzed Finnish children from 6 months to13 years old, comparing vaccinating all children to vaccinating high risk children only (Salo, Kilpi, Sintonen, Linna, Peltola, & Heikkinen, 2006). Risk was defined as the risk of influenza infection and respiratory complications. Age subgroups were defined in the evaluation: 6 months to 3 years old, 3 to 5 years old, 5 to 7 years old, and 7 to 13 years old. The Salo study estimated the number of children in Finland and used influenza incidence estimates from previous literature to approximate the number of children who would be infected. Taking this value, Salo et al. then applied a reduction of 80% (the assumed vaccine efficacy) across all health outcomes to determine the number of cases of health outcomes averted by vaccination. This is likely to result in an over-estimate of the effectiveness of the vaccine as the vaccine would only result in a reduction in the actual cases of influenza. It is unlikely that the vaccine would have the same degree of efficacy on AOM. Salo et al. used Finnish national registries, published studies, and expert panel opinion to create estimates on the use of health care resources and unit costs associated with cases of influenza and associated outcomes (such as AOM). The number of averted cases and associated reduced health resource uses were then multiplied by the unit costs to generate total estimates of reduced health care resource costs for each comparator arm. The Salo study included direct costs for vaccine purchases and administration, as well as for health resource use as stated above. These included physician visits, antibiotics, and hospitalizations. Outpatient costs for the treatment of AOM and pneumonia antimicrobial therapy were also included; however, mild symptoms of influenza and any adverse effects of the vaccine were considered transient and excluded. In the CBA, Salo et al. only account for lost productivity time losses and did not monetize health outcomes. Vaccine costs were estimated at €2.20 per unit, with 10 minutes of nurse time (at €18.50 per hour) required for administration. Physician visits cost €58.50 per visit and hospitalizations cost €210.50 per stay. Indirect costs such as lost work days were estimated and included. Salo et al. did not include the possibility that an infected child would potentially transmit the infection within the household, but did assume that giving care for an infected child would cause the parent to take a formal sick day

from work, valued at €166.70 per day lost. These lost productivity costs were determined by the human capital approach valuing time using the average Finnish gross income. The incidence of influenza was assumed to be 16% of the pediatric population (121,885 cases from the 756,000 Finnish children, 6 months to 13 years of age). The outcome in this study was a composite of multi-factorial influenza related outcomes: AOM, pneumonia, sinusitis, severe illness (outpatient and inpatient), and uncomplicated symptomatic episodes. Vaccine efficacy was estimated at 80% and was applied across all outcomes. This multi-factorial outcome may overestimate the actual number of influenza cases in this population; it may be possible that children with AOM or sinusitis did not have influenza at all, but suffered these “influenza associated” outcomes in the absence of an influenza infection.

The results of the Salo study found that vaccinating all children across all subgroups, 6 months to 13 years of age, compared to vaccinating only high risk children was a more effective and less costly strategy.

The Navas study, which conducted both a CEA and a CBA, studied a hypothetical cohort of 1,000 Spanish children 3 to 14 years of age, a slightly older age group than in the Salo study, over a time horizon of 6 months (Navas, et al., 2007). This economic evaluation compared routinely vaccinating all children in primary care to no vaccination. All medical costs and were determined using the Catalan Health Service database and productivity costs were calculated with the human capital approach using an average daily salary in Spain. The study included costs for the vaccination program which included vaccine unit costs, administration, and transportation cost, but no health outcomes were monetized. Only lost productivity and health resource use cost was used in the analysis. The study did not include a willingness-to-pay exercise to determine the value of avoiding infections, hospitalizations, or deaths. Vaccine costs were estimated at €4.35 per unit, with €5 required for administration. Health resource use cost for the treatment of influenza infection consisted of physician visits, hospitalizations, and antibiotic/antipyretic consumption. Physician visits cost €32 per pediatrician visit; antibiotic and antipyretic use cost €7.8 and €2.7 respectively. Hospitalizations cost €3,159.75 per stay. The study also included lost productivity for a mother to care for an infected child. Only mothers were considered to be involved in care giving. Productivity costs included lost employment days (€59.06 per day lost) and included a lost work year if a child suffered a premature death (€10,662 for loss of a child).

The incidence of influenza associated health events such as acute febrile respiratory illness, hospitalizations, and deaths were determined from previous literature. Vaccine effectiveness was applied across all health events to the vaccinated arm: 58.6% reduction of acute febrile respiratory illness, 45.2% reduction of pediatric visits to a physician, 18.6% reduction of antibiotics and antipyretics use, and 33.3% reduction of work absenteeism. These outcomes were proxy outcomes used in lieu of the reduction of actual cases of influenza infection in this theoretical cohort. Using these values, Navas et al. then subtracted the number of events and associated health resource costs in the vaccinated arm to the non-vaccinated arm to determine the cost-benefit of the vaccination program.

The Navas study demonstrated that vaccinating all children compared to not vaccinating was cost saving to the amount of €7,587.03 for the cohort of 1,000 children in 2004 Euros. Similar to the Salo study, the result from the Navas study was a dominant strategy. From the Salo and Navas studies, despite the differences in inputs, comparator, and even geography, vaccinating adolescents generally was found to be cost-saving for society.

In another evaluation of older children, the Schmier study compared a school-based immunization program to no school-based immunization program in the United States(Schmier, Li, King, Nichol, & Mahadevia, 2008). The population of interest was school age children between 5 to 18 years old. The economic evaluation was alongside a large multi-state efficacy trial, so costs and health outcomes were derived directly from the trial. The efficacy trial used household surveys to determine vaccine efficacy and as such, a household was used as the unit of analysis in the economic evaluation instead of a single child, since it was possible that multiple children from the same household could attend the same school.

Health resource use was valued by applying unit prices from the published literature (Medical Fees in the United States database, Redbook drug prices) to utilization volume quantities from the clinical trial. Schimier et al. included costs for vaccine administration within a school-based context and also added special supplies needed for a school-based immunization program such as student photocopies of information booklets, standing orders, sharps containers, and humidifiers. Vaccine cost was estimated at $17.95USD per unit, with $2.75USD of nurse time (at $41.32USD per hour) required for administration.

Since vaccine efficacy measures were based only on the household survey responses, only health resource use costs and lost productivity were included in the CBA and no monetizing of outcomes was performed. Health resource use associated with infection included physician visits at $76USD per visit and hospitalizations $4,653USD per stay for children and $7,578USD per stay for adults. Other medication unit costs for symptomatic management of an infection consisted of over-the-counter medications ($3.93USD), prescription medications ($26.75USD), and herbal remedies ($4.89USD).

Schimier et al. assumed that an infected child would cause a single adult within the household to take a formal day from work for care giving, but did not factor in possible infection of the adult. Productivity costs included lost employment days ($214.88USD per day lost), lost unspecified days ($147.18USD per day lost), and lost school days ($25USD per day lost). The lost school days were based on the author's calculations from the Chalkboard Project, which provided a framework for the estimated value of a school day in the United States (Chalkboard Project, 2010).

The incidence of circulating influenza was determined to be approximately 17% across the four U.S. states where the schools were located. The health outcome used to define vaccine effectiveness was case of ILI. This value was reported by household survey. Vaccine effectiveness of the immunization program was a 35% reduction of ILI in households that had at least one vaccinated child.

The Schimier study found that a school-based immunization program compared to no school-based immunization program resulted in a net societal benefit of $171.96USD per household vaccinated, in 2006 United States dollars. Similar to the Luce study and Cohen study, the Schimier study reinforces that programs (such as school-based immunization) which minimize time off work for parents are more likely to be cost-saving for society.

3.3.2.2 Health Care System Perspective

From the health care system perspective, Marchetti et al., Saloet al., Navas et al., and Pitman et al. studied healthy children from 6 months to 18 years old (Marchetti, Kühnel, Colombo, Esposito, & Principi, 2007; Salo, Kilpi, Sintonen, Linna, Peltola, & Heikkinen, 2006; Navas, et al., 2007; Pitman, Nagy, & Sculpher, 2013). The Marchetti study and Pitman study were

conducted as CUAs; the Salo study and Navas study were conducted as CBAs. The studies were published between 2006 and 2012.

The study designs and populations studied by Marchetti et al., Salo et al., and Navas et al. were described in the previous societal perspective section. The major difference compared to the societal perspective was that the health care system perspective excluded productivity costs for parents and caregivers. This has a substantial impact on ICERs.

From the health care system perspective, the Marchetti study found that vaccinating all children aged 6 to 60 months and 6 to 24 month resulted in an incremental cost of €10,000 per QALY gained and €13,333 per QALY gained respectively, when compared to vaccinating high risk children of the same age groups. The incremental cost for the 6 to 24 month subgroup was slightly higher because the QALYs gained were fewer than in the 6 to 60 month old subgroup. These results clearly differ from the societal perspective, where vaccinating all children was found to be a dominant strategy across both subgroups.

The Salo study found that vaccinating all children 6 months to 13 years old compared to only vaccinating high risk children was dominant in the health care system's perspective. This was the case in all age subgroups, but the savings were more pronounced in the younger children. While these results are in the same cost-effectiveness quadrant as the societal perspective, the incremental net savings were less evident.

In the Navas study, the results from the health care provider perspective differed from the dominant strategy seen from the societal perspective. Vaccinating a healthy cohort of 1,000 hypothetical children compared to not vaccinating these children resulted in a net cost of €1,460.51. By excluding productivity losses, this perspective resulted in a cost of €5.80 per acute febrile event avoided and €18.26 per QALY gained, shifting from a lower incremental cost and higher incremental effectiveness quadrant to a higher incremental cost and a higher incremental effectiveness quadrant.

Pitman et al. only performed an economic evaluation from the health care system perspective, studying healthy children from England and Wales aged 2 to 18 years (Pitman, Nagy, & Sculpher, 2013). The analysis compared vaccinating all children to the standard policy of vaccinating only high risk children. Three age subgroups were defined within the study: children

2 to 4 years old, 2 to 10 years old, and 2 to 18 years old. This economic evaluation was the only one included in this review to incorporate a dynamic transmission model, where herd immunity effects were modeled and accumulated across the population over a long timeframe. This model was run with a time horizon of 200 years for the population, longer than any other included economic evaluation; for the individual level, the time horizon was taken as an individual's lifetime with a life expectancy of 84 years. Pitman et al. demonstrated that the incremental cost per QALY remains constant after approximately 150 to 200 years of modeling. This was the rationale for a 200 year horizon allowing for discounted costs and benefits to fully accrue over time (Pitman, Nagy, & Sculpher, 2013).The Pitman study examined two vaccines: TIV and LAIV with vaccination occurring every season. Results were cumulative over the 200 year period.

Costs for vaccination consisted of unit vaccine cost, primary care administration, and dispensing fee. Vaccine costs were estimated at £5.81 per unit, with £1.81 dispensing fee, £0.03 container cost, £0.61 cost allowance, and a £31 per GP visit required for administration. Health resource use costs associated with infection were physician visits, hospitalizations and prescription antibiotics. Physician visits to treat infection cost £79.77 per GP visit using an average price across all age groups, and hospitalizations due to infection cost £2,123 per visit using an average price across all age groups. Costs and resource use inputs were derived from previous literature and governmental databases such as the British National Formulary for treatment and drug prices and the National Health Services Costing and Cost Collection database for unit costs of hospitalizations.

QALYs were used as a health outcome in this study. Utility scores were taken from previous literature which conducted visual scales and time-trade off surveys (Turner, Wailoo, Nicholson, Cooper, Sutton, & Abrams, 2003). Several additional parameters were also incorporated into this study due to the dynamic transmission model, such as basic reproductive rate (R_o), duration of natural and vaccine-related immunity, and population mixing. These parameters were necessary in order to simulate the effects of vaccination on the entire population over a long time horizon. Effects included transmission of influenza from children to others in the population as well as the herd immunity effects that would occur with mass vaccination. The basic reproductive rate is a measure of the transmission potential for an infectious disease. R_o is the expected number of new secondary cases produced within a completely susceptible population from a single infected individual (Dietz, 1993). If this value is less than 1, the infectious disease

is self-limiting and eventually disappears from the population; if this value is greater than 1, the disease will continue to self-propagate and spread. In this study, the rate of 1.8 was used to simulate the incidence of influenza cases in the population (Pitman, Nagy, & Sculpher, 2013).

Health outcomes used to define vaccine efficacy were infection leading to a symptomatic case of influenza or death. Vaccine effectiveness was not clearly defined but was assumed to be 80%reduction in influenza cases (unspecific to ILI or LCI) for LAIV in children 2 to 18 years old, and 60%, 50%, and 75% reduction in influenza cases for TIV in children, elderly, and adults 19 to 64 years respectively. The assumed uptake for the vaccine was set at 50%.

The results of the Pitman study demonstrate the differences in incremental costs among age subgroups. Providing TIV to all children was incrementally more costly than the standard policy of vaccinating only high risk children, but resulted in improved health outcomes. The incremental costs in 2012 British pounds were £192 per QALY gained for children 2 to 4 years, £403 per QALY gained for children 2 to 10 years, and £429 per QALY gained for children 2 to 18 years old. A similar pattern of results emerged for the LAIV but the benefits were more pronounced due to greater effectiveness of LAIV in children. Using LAIV resulted in a dominant strategy for children 2 to 4 years of age and incremental costs in 2012 British pounds of £225 per QALY gained for children 2 to 10 years old, £252 per QALY gained for children 2 to 18 years. This correlation between increasing age and increasing incremental cost was also seen in the Prosser study. This is likely due to a combination of a higher risk of infection in younger children as well as superior vaccine effectiveness and associated greater health improvement in younger children compared to older children, at a relatively constant vaccination cost.

3.3.2.3 Third Party Payer Perspective

Only the Luce study performed an analysis from the third party payer perspective (Luce, et al., 2001). As detailed in the earlier societal perspective section, the Luce study evaluated a group-based or an individual-based vaccination program for children aged 15 to 71 months. Both the group and individual-based scenarios compared to no vaccination at all had an ICER of $19.10USD per ILI fever day avoided in 1998 US dollars. The same values were observed for the two scenarios because the third party is only involved in the direct medical costs of the vaccination, regardless of administration setting. This result is slightly higher than the societal perspective where all medical costs, such as hospitalization costs and benefits, such as reduced productivity losses are included in the analysis.

3.3.2.4 Family and Individual Perspective

Salleras et al. and Esposito et al. applied family and individual perspectives to their economic evaluations (Salleras, et al., 2009; Esposito, et al., 2006). While the Esposito study mentioned an individual perspective evaluation in its methods, it did not report the individual perspective results separately from the societal perspective results.

The Salleras study was a CBA in Spain that compared vaccinating a hypothetical cohort of 1,000 children 3 to 14 years old to not vaccinating over a 6 month time horizon. The only perspective studied was the family perspective. Included were costs for vaccination with vaccine costs estimated at €13.73 per unit and €5 required for administration.

Direct medical costs of infection were provided by paediatricians participating in a prospective cohort study (Salleras, et al., 2006). The cost of the private paediatric visit and of treatment with antibiotics and antipyretics for an acute febrile respiratory process were used in this model. Physician visits cost €40 per pediatrician visit and out-of-pocket treatment costs such as the use of antibiotics and antipyretics were estimated at €7.80 and €2.70 per episode of use, respectively.

Lost work days and travel time were calculated for caregivers using the human capital approach considering that the value of time lost was equivalent to the value of lost productivity. One lost work day was valued at €40 per day and a lost school day was valued at €20 per day.

As a CBA, Salleras et al. calculated the number of acute febrile respiratory illnesses, which was used as a proxy indicator of influenza infection, and associated resource use in each arm of the study. The difference between the vaccinated arm and the non-vaccinated arm was determined for the cost benefit analysis. The CBA also included a willingness-to-pay exercise where Salleras et al. reported that parents were willing to pay €20 and €40 to avoid a day of school absenteeism or work absenteeism respectively as a result of an acute febrile paediatric respiratory process. These values were incorporated into the CBA as indirect costs of an influenza infection but are not accounted for in the denominator of the ICER equation as a benefit of vaccination. An assumed vaccine effectiveness was taken from previous literature and applied across the health outcome (58.6% reduction on acute febrile respiratory illness) as well as associated health resource use (45.2% reduction in pediatric visits, 18.6% reduction in antibiotics/antipyretics use). Reductions in indirect costs were also factored into the cost benefit

analysis (57.8% reduction in lost school days, and 33.3% reduction in lost work days). The result for this hypothetical cohort of children and their families was a net savings of €21,551.62 in year 2000 Euros.

Table 16: Data Extraction for Children and Adolescents

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Cost Items	Health Outcomes
Cohen, 2000	Healthy children, 6months - 5 years	Societal	CBA	USA	Not reported	USD, Not reported	Decision Model	Vaccination, flexible and restricted setting	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, absenteeism, lost work days	Cases of LCI, AOM
Esposito (Societal), 2006	Healthy children, 2-5 years	Societal	CBA	Italy	Single flu season	EUR, 2003, no mention	Alongside RCT	Vaccination	No vaccination	Vaccine, administration, Absenteeism	Influenza-like morbidity: Cases of URI, LRI, febrile respiratory illness, hospitalizations, number of antibiotics, antipyretics, missed school days
Luce (Societal, group), 2001	Healthy children 15 - 71 months	Societal	CEA	USA	Two flu seasons	$USD, 1998, 3%	Alongside trial	Vaccination for all children - group setting	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, caregiving, patient time, travel costs	ILI fever days
Luce (Societal, individual), 2001	Healthy children 15 - 71 months	Societal	CEA	USA	Two flu seasons	$USD, 1998, 3%	Alongside trial	Vaccination for all children - individual setting	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, caregiving, patient time, travel costs	ILI fever days
Marchetti (Societal), 2007	Healthy children, 6 - 60 months, 6 - 24 months	Societal	CUA	Italy	5 years	EUR, 2004, 3%	Decision Model with Markov Model	Vaccination for all children	Vaccination for high risk children only	Vaccine, administration, physician visits, hospitalization, treatment/drug, lost work days, caregiver costs	ILI and ILI related events (AOM, lower respiratory tract infection)
Navas (Societal), 2007	Healthy children, 3-14 years	Societal	CBA/CEA	Spain	6 months	EUR, 2004, None, except for deaths at 5%	Decision model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, caregiving, Lost work days	Acute febrile respiratory processes, hospitalizations, deaths, pediatric visits, antibiotics, antipyretics, absenteeism

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; URI = upper respiratory illness; LRI = lower respiratory illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 16: Data Extraction for Children and Adolescents, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Cost Items	Health Outcomes
Salo (Societal), 2006	Healthy children, 6 months - 13 years	Societal	CBA	Finland	Not reported	EUR, 2004, no mention	Decision Model	Vaccination for all children	Vaccination for high risk children only	Vaccine, administration, physician visits, hospitalization, treatment/drugs, travel costs, lost work days	Cases of influenza related outcomes (AOM, pneumonia, sinusitis, severe illness (outpatient and inpatient), uncomplicated
Prosser TIV, 2006	Healthy children 6 - 23 mo, 2y, 3-4y, 5-11y, 12-17yrs	Societal, inferred	CUA	USA	One year	$USD, 2003, no mention	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drug, lost work day	Influenza episodes, hospitalizations, deaths, and QALYs
Prosser LAIV, 2006	High risk children 6 - 23 mo, 2y, 3-4y, 5-11y, 12-17yrs	Societal, inferred	CUA	USA	One year	$USD, 2003, no mention	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drug, lost work day	Influenza episodes, hospitalizations, deaths, and QALYs
Schmier, 2008	Healthy school children, 5-18 years	Societal, inferred	CBA	USA	Single flu season	$USD, 2006, no need for discounting	Alongside non-RCT	Vaccination for all schoolchildren	No school-based vaccination (but could vaccinate outside of school)	Vaccine, administration, standing orders, physician visits, hospitalization, treatment/drugs, other supplies, transportation, lost work days, lost school days, travel costs	Cases of ILI
Marchetti (HCS), 2007	Healthy children, 6 - 60 months. 6 - 24 months	Health Care System	CUA	Italy	5 years	EUR, 2004, 3%	Decision Model with Markov Model	Vaccination for all children	Vaccination for high risk children only	Vaccine, administration, physician visits, hospitalization, treatment/drug	ILI and ILI related events (AOM, lower respiratory tract infection)
Navas (HCS), 2007	Healthy children, 3-14 years	Health Care System	CBA	Spain	6 months	EUR, 2004, None, except for deaths at 5%	Decision model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, caregiving	Acute febrile respiratory processes, hospitalizations, deaths, pediatric visits, antibiotics, antipyretics, absenteeism

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros; HCS = health care system

Table 16: Data Extraction for Children and Adolescents, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Vaccination Costs Medical Costs Productivity Costs	Health Outcomes
Pitman TIV, 2012	Healthy children, 2 - 18 years	Health Care System	CUA	England & Wales	200 years	£, 2012, 3.5%	Dynamic Transmission Model	Vaccination for all children	Vaccination for high risk children only	Vaccine, administration, physician visits, hospitalization, treatment/drug	Cases of ILI (symptomatic case, GP consult, hospitalization, death) to determine QALYs
Pitman LAIV, 2012	Healthy children, 2 - 18 years	Health Care System	CUA	England & Wales	200 years	£, 2012, 3.5%	Dynamic Transmission Model	Vaccination for all children	Vaccination for high risk children only	Vaccine, administration, physician visits, hospitalization, treatment/drug	Cases of ILI (symptomatic case, GP consult, hospitalization, death) to determine QALYs
Salo (HCS), 2006	Healthy children, 6 months - 13 years	Health Care System	CBA	Finland	Not reported	EUR, 2004, no mention	Decision Model	Vaccination for all children	Vaccination for high risk children only	Physician visits, hospitalization, treatment/drug	Cases of influenza related outcomes (AOM, pneumonia, sinusitis, severe illness (outpatient and inpatient), uncomplicated
Luce (TPP, group), 2001	Healthy children 15 - 71 months	Third Party Payer	CEA	USA	Two flu seasons	$USD, 1998, 3%	Alongside trial	Vaccination for all children - group setting	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, caregiving, patient time, travel costs	ILI fever days
Luce (TPP, individual), 2001	Healthy children 15 - 71 months	Third Party Payerl	CEA	USA	Two flu seasons	$USD, 1998, 3%	Alongside trial	Vaccination for all children - individual setting	No vaccination	Vaccine, administration, physician visits, hospitalization, treatment/drugs, caregiving, patient time, travel costs	ILI fever days

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros; TPP = third party payer

Table 16: Data Extraction for Children and Adolescents, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Vaccination Costs Medical Costs Productivity Costs	Health Outcomes
Salleras, 2009	Healthy children, 3-14 years	Family	CBA	Spain	6 months	EUR, 2000, no need for discounting	Mathematical Equation	Vaccination	No vaccination	Vaccine, administration, physician visits, treatment/drugs, lost work/school day, time, travel costs	Acute febrile respiratory processes, hospitalizations, deaths, pediatric visits, antibiotics, antipyretics, absenteeism
Esposito (Individual), 2006	Healthy children, 2-5 years	Individual	CBA	Italy	Single flu season	EUR, 2003, no mention	Alongside RCT	Vaccination	No vaccination	Vaccine, administration, Absenteeism	Influenza-like morbidity: Cases of URI, LRI, febrile respiratory illness, hospitalizations, number of antibiotics, antipyretics, missed school days

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; URI = upper respiratory illness; LRI = lower respiratory illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 17: Results for Children and Adolescents

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Cohen G, 2000	$1.20 benefit vs. Restricted setting; $21.28 benefit vs. Flexible setting	83% reduction in LCI cases, 32% reduction in AOM	$1.20 benefit vs. Restricted setting; $21.28 benefit vs. Flexible setting	Did not report costing year
Esposito (Societal), 2006	€131.43/child	URI: -33% LRI: -22%, FRI:-26%, Hospitalizations:-50%, Antibiotics: -32%, Antipyretics: -29%, Missed school days: -48%	€131.43/child vaccinated, cost saving	$258.80CAD/vaccination cost saving
Luce (Societal, group), 2001	Not reported	1.2 fewer ILI days/child	Dominant	Dominant
Luce (Societal, individual), 2001	Not reported	1.2 fewer ILI days/child	$29.67/ILI fever day avoided	$56.93CAD/ILI fever day avoided
Marchetti (Societal), 2007	1) 6-24 month olds - €7/child. 2) 6-60 month olds -€21/child	1) 6-24 month olds 0.05 events, 0.0003 QALYs. 2) 6-60 month olds 0.16 events, 0.0010 QALYs.	Dominant for both age groups	Dominant for both age groups
Navas (Societal), 2007	€ 17,012.03	Acute febrile process - episodes: 251.6, hospitalizations: 0.1758, deaths: 0.0012; pediatric visits 212.5, antibiotics: 58.0; antipyretics: 58.0; work absenteeism: 158.5	NPV = +€7587.03, cost-benefit ratio 1.80. Dominant for febrile events and QALY.	NPV = +$14,409.87CAD, cost-benefit ratio 1.80. Dominant for febrile events and QALY.
Salo (Societal), 2006	6mo to <3yrs: €2804295, 3 to <5yrs: €3442018, 5 to <7yrs: €3617380, 7 to 13 yrs: €1192131	6mo to <3yrs: 5056 cases, 3 to <5yrs: 3961 cases, 5 to <7yrs: 3961 cases, 7 to 13 yrs: 11399 cases	Cost-saving, dominant for all age groups	Cost-saving, dominant for all age groups

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; URI = upper respiratory infection; LRI = lower respiratory infection; FRI = febrile respiratory illness; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros; LAIV = live attenuated intranasal vaccine; NPV = net present value

Table 17: Results for Children and Adolescents, Continued

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Prosser TIV, 2006	Low risk: 6-23 mo: $37,000, 2y: $43,000, 3-4y: $47,000, 5-11y: $44,000, 12-17yo: $44,000. High risk: 6-23mo: -$74,000, 2y: -$22,000, 3-4y: $2,000, 5-11y: $12,000, 12-17y: $13,000	Low risk: 6-23 mo 3.0 QALY gained, 2y: 2.4 QALY gained, 3-4y: 1.7 QALY gained, 5-11y: 0.6 QALY gained, 12-17yo: 0.4 QALY gained. High risk: 6-23 mo 7.2 QALY gained, 2y: 5.4 QALY gained, 3-4y: 4.0 QALY gained, 5-11y: 1.6 QALY gained, 12-17yo: 1.3 QALY gained	Low risk: 6-23 mo: $12000/QALY, 2y: $18000/QALY, 3-4y: $28000/QALY, 5-11y: $79000/QALY, 12-17yo $119000/QALY. High risk: 6-23mo: Dominant, 2y: Dominant, 3-4y: $1000/QALY, 5-11y: $7000/QALY, 12-17y: $10000/QALY	Low risk: 6-23 mo: $22322CAD/QALY, 2y: $33483CAD/QALY, 3-4y: $44021CAD/QALY, 5-11y: $124204CAD/QALY, 12-17yo $221364CAD/QALY. High risk: 6-23mo: Dominant, 2y: Dominant, 3-4y: $1860CAD/QALY, 5-11y: $13021CAD/QALY, 12-17y: $18600CAD/QALY
Prosser LAIV, 2006	Low risk: 6-23 mo: $32,000, 2y: $42,000, 3-4y: $50,000, 5-11y: $48,000, 12-17yo: $49,000	Low risk only: 6-23 mo 3.7 QALY gained, 2y: 2.9 QALY gained, 3-4y: 2.1 QALY gained, 5-11y: 0.7 QALY gained, 12-17yo: 0.5 QALY gained	Low risk only: 6-23 mo $9000/QALY, 2y: $15000/QALY, 3-4y: $25000/QALY, 5-11y: $72000/QALY, 12-17yo: $109000/QALY	Low risk only: 6-23 mo $16879CAD/QALY, 2y: $28135CAD/QALY, 3-4y: $46892CAD/QALY, 5-11y: $135047CAD/QALY, 12-17yo: $204447CAD/QALY
Schmier, 2008	-$171.96/household	-9% of households had ILI	Savings of $171.96/household (based on cohort of 1000 households)	Savings of $221.47CAD/household (based on cohort of 1000 households)
Marchetti (HCS), 2007	1) 6-24 month olds + €4/child. 2) 6-60 month olds +€10/child	1) 6-24 month olds 0.05 events, 0.0003 QALYs. 2) 6-60 month olds 0.16 events, 0.0010 QALYs.	vs. No vaccination €13333/QALY for 6 - 24 mo. €10000/QALY for 6 - 60 mo.	vs. No vaccination - $21740CAD/QALY for 6 - 24 mo. $18933CAD/QALY for 6 - 60 mo.
Navas (HCS), 2007	€ 7,964.49	Acute febrile process - episodes: 251.6, hospitalizations: 0.1758, deaths: 0.0012; pediatric visits 212.5, antibiotics: 58.0; antipyretics: 58.0; work absenteeism: 158.5	NPV = -€1460.51, €5.80/acute febrile event avoided, €18.26/QALY	NPV = -$2,773.92CAD, $11.02CAD/acute febrile event avoided, $34.68CAD/QALY
Pitman TIV, 2012	Vs. Current policy: £192 if 2-4 years included, £1554 if 2-10 years included, £1218 if all children 2-18yo included	Vs. Current policy: +1.6QALY if 2-4 years included, +3.8QALY if 2-10 years included, +6QALY if all children 2-18yo included	Vs. Current policy: £192/QALY if 2-4 years included, £403/QALY if 2-10 years included, £429/QALY if all children 2-18yo included	Vs. Current policy: $309CAD/QALY if 2-4 years included, $649CAD/QALY if 2-10 years included, $691CAD/QALY if all children 2-18yo included

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros; NPV = net present value; HCS = health care system

Table 17: Results for Children and Adolescents, Continued

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Pitman LAIV, 2012	Vs. Current policy: -£182M if 2-4 years included, £1152M if 2-10 years included, £699M if all children 2-18yo included	Vs. Current policy: +2QALY if 2-4 years included, +4.3QALY if 2-10 years included, +6.6QALY if all children 2-18yo included	Vs. Current policy: dominant if 2-4 years included, £225/QALY if 2-10 included, £252/QALY if all children 2-18yo included	Vs. Current policy: dominant if 2-4 years included, $356CAD/QALY if 2-10 included, $399CAD/QALY if all children 2-18yo included
Salo (HCS), 2006	6mo to <3yrs: €1720654, 3 to <5yrs: €963360, 5 to <7yrs: €678594, 7 to 13 yrs: €915672	6mo to <3yrs: 5056 cases, 3 to <5yrs: 3961 cases, 5 to <7yrs: 3961 cases, 7 to 13 yrs: 11399 cases	Cost-saving, dominant for all age groups	Cost-saving, dominant for all age groups
Luce (TTP, group), 2001	Not reported	1.2 fewer ILI days/child	$19.10/ILI fever day avoided	$36.66CAD/ILI fever day avoided
Luce (TTP, individual), 2001	Not reported	1.2 fewer ILI days/child	$19.10/ILI fever day avoided	$36.66CAD/ILI fever day avoided
Salleras, 2009	€21,551.62 for cohort of 1000 children	251.6 acute febrile events	€21,551.62 total, net benefit	$39,466 CAD total, net benefit
Esposito (Individual), 2006	Not reported	URI: -33% LRI: -22%, FRI:-26%, Hospitalizations:-50%, Antibiotics: -32%, Antipyretics: -29%, Missed school days: -48%	Not reported	Not reported

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; URI = upper respiratory illness; LRI = lower respiratory illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

3.3.3 High Risk Groups

Four studies were specific to high risk groups (risk in this case was related to complications of influenza rather than risk of infection) including elderly adults (>65 years old) or those with underlying comorbidities or cancer. Risk in this case was related to complications due to influenza infection. Additionally, health care workers aged 20 to 65 years old who are at higher risk of infection were also studied. Of these four studies, one was excluded after quality appraisal, leaving three studies that were included in the analysis (Avritscher, et al., 2007; Nichol & Goodman, 2002; Blommaert, Bilcke, Vandendijck, Hanquet, Hens, & Beutels, 2014).

Two studies were based in the United States and were conducted from the societal perspective and the other study was based in Belgium and was conducted from the health care system perspective. The analytic techniques were CUA, CBA, and CEA. The Avritscher study examined a special population of working age cancer patients, aged 20 to 64 years old, while the Nichol 2002 study focused on elderly individuals 65 to 74 years old. The Blommaert study evaluated two specific high risk groups: health care workers aged 20 to 65 years and people with underlying illnesses (asthma, cardiovascular disease, diabetes, human immunodeficiency virus (HIV), hypertension, and stroke). Table 18 summarizes the results for high risk groups in a cost-effectiveness plane.

Table 18: Cost-effectiveness Summary for High Risk Groups

		Incremental Effectiveness	
		-	**+**
Incremental Costs	**+**		• Avritscher • Blommaert
	-		• Nichol

3.3.3.1 Societal Perspective

The Avritscher study compared vaccinating working age cancer patients to not vaccinating working age cancer patients over a time horizon of one year (Avritscher, et al., 2007). The base case patient was a 51 year old within five years of cancer diagnosis, chosen because it is the mean age and length of cancer diagnosis as per the United States National Cancer Institute.

Costing for this study was for influenza-related costs specifically for this patient type, determined through custom surveys with oncologists. Costs for vaccination, including administration were estimated at $11USD per unit. Treatment costs related to influenza infection for over the counter drugs and antivirals were also calculated. Physician visits cost $29USD per visit; hospitalizations were valued at $1,197USD per stay for incident cancer patients (i.e. those who have been just diagnosed) and $774USD per stay for patients previously diagnosed with cancer. Pharmaceutical use was estimated at $74USD for antiviral medication and $6USD for over the counter medications.

As these patients were still of working age, productivity losses were based on the average gross income as per United States census. Productivity losses were set to $14USD per lost work hour as per the mean per capita income for this population by age obtained from the 2000 U.S. Census, adjusted to 2005 dollars.

Vaccine effectiveness was taken from previous literature, estimated at a 32% reduction in incident cases of influenza. This estimated value incorporated an anticipated reduction in vaccine efficacy in this patient type. Health outcomes in the Avritscher study were incident cases of influenza, death, and QALYs. Utility weights were derived from a published study where the utility weight for a day with influenza symptoms was determined using the Quality of Well Being Scale (Mauskopf, Cates, Griffin, Neighbors, Lamb, & Rutherford, 2000). These utilities were then applied to the mean number of days associated with influenza infection. In addition to this utility weight for influenza infection, the utility weights for malignancies were taken from a study (O'Leary, Fairclough, Jankowski, & Weeks, 1995) that used the time-trade-off method to derived utility scores to estimated life expectancies of an average cancer patient. Base case incidence of influenza was assumed to be 10% for this population.

The results from the Avritscher study demonstrated that compared to no vaccination, vaccinating working age cancer patients resulted in an incremental cost of $224USD per QALY gained in 2005 United States dollars.

The Nichol 2002 study examined the cost-effectiveness of vaccinating elderly adults (>65 years old) compared to no vaccination using CBA and CEA. This study included costs for vaccine and administration estimated at $7.93USD per unit. Direct medical treatment costs for infection were included hospitalizations at $7,657USD per visit; however surprisingly, physician visits and other

treatment costs were not included. No monetization of health outcomes was performed which meant that only health care costs and not monetized benefits were included in the analysis. Lost productivity costs were included, as the author claimed that a greater number of elderly adults continue to participate in the workforce or engage in housekeeping, and estimated at $5.82USD per lost work hour. This value was adjusted and weighted by age distribution of the persons included in the study and by the estimated proportion still in the labor force, in the housekeeping force, and in retirement.

Health resource unit costs and quantity used were taken from the Group Health Inc. claims database, the literature, and from current reimbursement prices from the United States Medicare database. Group Health Inc. is health maintenance organization in the Minneapolis, St. Paul, Minnesota area. Health resource use was used as a proxy measure for health outcomes, and no specific case definition of infection was used to determine vaccine efficacy. Reductions in health resource use were applied as a measure of efficacy. Vaccination was associated with a 36% reduction in hospitalizations due to pneumonia and influenza, an 18% reduction in hospitalizations due to acute and chronic respiratory conditions. Aside from health resource measures, deaths (health outcome) were estimated for this study. Vaccination was assumed by the author to reduce deaths by 40%.

The results of providing vaccination to a cohort of 10,000 elderly adults were a net societal savings of $429,008USD per 10,000 persons vaccinated. In terms of cost per life saved, this was calculated and found to be $53,652 USD per life saved in 1996 United States dollars.

The Blommaert study evaluated two specific high risk groups: firstly, people with underlying illnesses (asthma, cardiovascular disease, diabetes, HIV, hypertension, stroke) of all ages, and secondly, health care workers aged 20 to 65 years old.
Vaccination occurred in the primary care setting. Additionally, for health care workers it was assumed an occupational health care professional could also administer the vaccine.

Current vaccine uptake for these groups was assumed to be 40% for high risk groups and 35% for health care workers. Costs included were vaccination and administration set at €23.30 per unit and hospitalization costs which ranged from €3,437 to €7,507 for high risk groups depending on the age of the individual and €2,513 to €5,664 for health care workers. Utilities

were determined as previously stated in section 3.3.1—from a previous study which used a VAS to gather utility weights and applied these to the duration of an influenza episode.

For those high risk groups with underlying disease, results were age stratified, with an incremental cost of €22,008 per QALY gained for those 0 to 14 years old, €24,768 per QALY gained for 15 to 49 year olds, and €14,378 per QALY gained for 50 to 64 year olds.

The results of the study also found that vaccinating health care workers compared to not vaccinating health care workers had an incremental cost of €24,096 per QALY gained, without including the potential indirect protection vaccination provides to others. If secondary protection was included, the result was likely to be cost-saving. This result demonstrates that vaccination of health care workers is cost-effective and for those with underlying disease, vaccination is also cost-effective.

Table 19: Data Extraction for High Risk Groups

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Vaccination Costs Medical Costs Productivity Costs	Health Outcomes
Avritscher, 2007	Cancer patients, 20-64 years	Societal	CUA	USA	1 year	$USD, 2005, 3% for QALYs, none for costs	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visit, hospitalization, treatment/drugs	QALYs
Nichol, 2002	Healthy elderly adults, 65 - 74 years	Societal	CBA and CEA	USA	Not reported	$USD, 1996, 5%	Mathematical Equation	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalizations, deaths, lost earnings	Hospitalization for pneumonia/influenza, hospitalization for acute/chronic respiratory conditions, death
Blommaert, 2014	Health care workers, 20 - 65 years	Health Care System	CEA	Belgium	1 year	EUR, no mention, no need for discounting	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalizations, deaths	QALYs, life expectancy
Blommaert, 2014	People with underlying illnesses (asthma, CV disease, diabetes, HIV, HTN, stroke), >50 years	Health Care System	CEA	Belgium	1 year	EUR, no mention, no need for discounting	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visits, hospitalizations, deaths	QALYs, life expectancy

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; CV = cardiovascular; HTN = hypertension; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 20: Results for High Risk Groups

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Avritscher, 2007	$2.24USD per patient	0.01QALYs	$224USD/QALY	$304USD/QALY
Nichol, 2002	$429,008 USD per 10000 persons vaccinated; $53,652 USD per life saved	36% reduction in HPI, 18% reduction in HACRC, 40% reduction in death	$429,008 USD per 10000 persons vaccinated - net benefit; $53,652 USD per life saved	$797,303 CAD per 10000 persons vaccinated - net benefit; $99,711 CAD per life saved
Blommaert, 2014	€709,703 for 239,740 cohort	3 hospitalizations prevented, 0.07 deaths prevented, 29 QALYs for 239,740 cohort	€24,096/QALY	$35,341/QALY
Blommaert, 2014	Age 0 - 14 years: €689,687 for 117,473 cohort. Age 15 - 49 years: €2,476,027 for 407,613 cohort. Age 50 - 64 years: €1,902,263 for 320,672 cohort.	Age 0 - 14 years: 10 hospitalizations 0.23 deaths prevented, 31 QALYs gained for 117,473 cohort. Age 15 - 49 years: 17 hospitalizations 1.02 deaths prevented, 100 QALYs gained for 407,613 cohort. Age 50 - 64 years: 21 hospitalizations 3.96 deaths prevented, 132 QALYs gained for 320,672 cohort.	Age 0 - 14 years: €22,008/QALY. Age 15 - 49 years: €24,768/QALY. Age 50 - 64 years: €14,378/QALY.	Age 0 - 14 years: €32,278/QALY. Age 15 - 49 years: €36,326/QALY. Age 50 - 64 years: €21,087/QALY.

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

3.3.4 Overall Population

Two studies evaluated universal influenza immunization programs (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011; Sander, et al., 2010). Both studies were included in the analysis after quality appraisal; the Clements study was acceptable and the Sander study was considered high quality.

The analytical technique for the two studies was CUA comparing a universal immunization program to a targeted immunization program only vaccinating high risk individuals. Risk was related to influenza infection and its complications. The Clements study was based in the United States with a time horizon of one year as well as an individual's lifetime to capture long term health outcomes and the Sander study was based in Canada with a time horizon of an individual's lifetime. This time horizon was used to capture QALYs lost to influenza-related death. The Clements study used a societal perspective for the entire United States population and the Sander study used a health care system perspective for the province of Ontario. Table 21 summarizes the results for overall population in a cost-effectiveness plane.

Table 21: Cost-effectiveness Summary for Overall Population

		Incremental Effectiveness	
		-	**+**
Incremental Costs	**+**		Sander
	-		Clements

3.3.4.1 Societal Perspective

Using a decision analysis model, the Clements study determined the cost-effectiveness per QALY gained (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011). Several model inputs were based on published literature and accessible U.S. databases such as the Centre for Disease Control website and the Physicians Fee Coding Guide for prices of vaccine and medical resource costs. Clements et al. estimated vaccine costs at $9USD to $19USD per unit and $23USD to $31USD per administration depending on age group. Health resource use unit

costs related to influenza treatment included physician visits, hospitalizations, and outpatient treatment costs. Physician visits were estimated from $254USD to $487USD per visit, depending on age group; hospitalizations were valued at $19,864USD to $30,515USD per stay, depending on age group. Antivirals were costed at $37USD to $75USD per episode, depending on age group. Lost productivity was also incorporated into this model. Productivity losses were $144USD per lost work day taken and applied from the United States Bureau of Labor Statistics.

The health outcomes measured in the Clements study were cases of ILI, hospitalizations, deaths, life years lost and QALYs. Hospitalizations were explicitly labeled as a clinical outcome. This study compared the number of cases of ILI, hospitalizations, deaths, life years lost and QALYs in each comparator arm and the difference between these comparators was used to determine the ICER. In this ICER calculation, the difference in health resource use costs (including hospitalizations) between the two arms were included in the numerator of the equation; the difference in QALYs between the two comparator arms were used in the denominator of the ICER equation.

Vaccination effectiveness was defined as reduction in ILI and ranged from 17.5%in adults to 36% in children. Life years lost due to ILI were estimated from the life expectancy of fatal cases. For the determination of QALYs, utilities were taken from previous literature which used surveys (EQ-5D, SF-12, VAS, Quality of Well Being Scale) to derive utility weights (Hanmer, Lawrence, Anderson, Kaplan, & Fryback, 2006).

Under the base case scenario, a universal immunization program for the United States population was a more effective and less costly strategy compared to the current targeted policy of vaccinating only high risk individuals. Across the United States population, the targeted vaccine program resulted in a cost of $114.5 billion USD, from 63 million ILI cases to 1.43 million hospitalizations, 148,000 deaths per year, and 859,000 expected lifetime QALYs while the universal mass vaccination resulted in costs of $111.4 billion USD, 61 million ILI cases, 1.36 million hospitalizations, 113,000 deaths per year, and 825,000 expected lifetime QALYs. Universal mass vaccination therefore saved $3.1 billion USD, averted 2 million ILI cases, 70,000 hospitalizations, 7,000 deaths, and gained 34,000 QALYs. The findings of this study suggest that universal mass immunization is both cost-saving and more effective in improving health outcomes across all age subgroups in the United States.

3.3.4.2 Health Care System Perspective

Sander et al. studied the population of Ontario from the health care system perspective (Sander, et al., 2010). Universal immunization was compared to a policy of vaccinating high risk individuals only. The time horizon was set to an individual's lifetime. Outcomes in the Sander study were cases of ILI, deaths, and QALYs.

A previous efficacy study evaluated and compared the effect of the Universal Influenza Immunization Program (UIIP) introduced in Ontario in 2001 to a targeted high-risk groups program (Kwong, et al., 2008). Effectiveness and resource use had been collected for three years before and four years after the introduction of UIIP, and the Sander study input this specific data from the Kwong study into the economic evaluation. Sander et al. provided unit costs for vaccine, administration, physician visits, hospitalizations, and outpatient treatment costs. Costs of communications and promotion strategies were also included in the analysis. Inputs were Ontario specific and were derived from population level health administrative data, a source for medical resource use (hospitalizations, physician and emergency department visits). Vaccine costs were $7.55CAD per unit. Health resource costs were based on the condition type (influenza, pneumonia) with physician visits $35CAD per office visit and $220CAD per emergency department visit. Hospitalizations were valued at $6,418CAD per stay inclusive of hospital physician charges. Utilities were taken from a previous study which surveyed participants and recalibrated Likert scores to utility weights (Turner, Wailoo, Nicholson, Cooper, Sutton, & Abrams, 2003). QALYs were then calculated by multiplying the duration of symptomatic period by the utility decrement associated with influenza infection. Since specific utility values were not available for children, the value for healthy adults was used.

Vaccinating the population of Ontario with UIIP resulted in 35,541 fewer cases of ILI, 111 fewer deaths, and 1,134 QALYs gained. The cost of this universal program was $12.24M CAD greater than the targeted program, resulting in an incremental cost of $10,797CAD per QALY gained in 2006 Canadian dollars. Overall these results suggest that UIIP was more costly but improved the health of the population more effectively than a targeted program for high risk individuals from the Ontario health care system perspective.

Table 22: Data Extraction for Overall Population

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Vaccination Costs Medical Costs Productivity Costs	Health Outcomes
Clements, 2011	Full population of United States	Societal	CUA	USA	1 year	$USD, not reported, 3%	Decision Model	Vaccination for all individuals	Vaccination for high risk individuals only	Vaccine, administration Physician visits, hospitalization, treatment/drugs, lost work day	Cases of ILI, hospitalizations, deaths, life years, QALYs
Sander, 2010	Full population of Ontario	Health Care System	CUA	Canada	Lifetime	$CAD, 2006, 3% for QALYs, none for costs	Decision Model	Vaccination for all individuals	Vaccination for high risk individuals only	Vaccine, administration, communication strategies, physician visits, hospitalization	Cases of ILI, deaths, QALYs

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 23: Results for Overall Population

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Clements, 2011	-$3,120M for United States population	-2417 ILI cases, -63 hospitalizations, -7 deaths, -43 life-years lost, -34 QALYs lost (all values in thousands)	Dominant	Dominant
Sander, 2010	$12.24M for Ontario population	-34541 cases, -111 deaths, +1134 QALYs	$10,797/QALY	$11,956CAD/QALY

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

3.3.5 Healthy Working Adults

Seventeen studies were specific to healthy working age adults. Of these, four were excluded and thirteen studies were included after quality appraisal. These studies were published between 2000 and 2007 including societal, health care system, third party payer, and employer perspectives. CUAs and CBAs were conducted. The age range of healthy working age adults was from 18 to 64 years with some studies specifically focusing on the 50 to 64 year age group.

Geographically, these studies were based in the United States, Australia, France, Italy, and Spain. Generally, time horizons in the studies were short, at approximately one flu season or a single year, with the exception of the Buxton-Bridges study which used time horizon of two flu seasons (Buxton-Bridges, et al., 2000). Four of the studies did not explicitly state a time horizon (Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006; Maciosek, Solberg, Coffield, Edwards, & Goodman, 2006; Nichol, 2001; Nichol, Mallon, & Mendelman, 2003) though it was inferable that a single year was used. Several studies explicitly stated a time horizon for the intervention (often a singly year or season) but implicitly used a lifetime time horizon for longer term outcomes. For instance, in the Aballéa study, costs and QALYs resulting from outcomes occurring during the intervention period were assessed over individuals' lifetimes. This effectively meant that the explicitly stated intervention time horizon was a single year, but that a second time horizon was used for outcomes as well.

The setting for the vaccine administration was diverse with this group. The majority of these publications studied administration in primary care by physicians and nurses, some studies incorporated specialist visits, and some were set in occupational or workplace clinics. In other studies, such as the Nichol study, administration was assumed to be in a broad base of locations including workplace clinics, community health clinics, and public clinics in drug stores and grocery stores (Nichol, 2001). The Buxton-Bridges study was conducted in a specific workplace (the Ford Motor Company, in Dearborn, Michigan) (Buxton-Bridges, et al., 2000). Table 24 summarizes the results for healthy working age adults in a cost-effectiveness plane.

Table 24: Cost-effectiveness Summary for Healthy Working Age Adults

		Incremental Effectiveness	
		-	+
Incremental Costs	+	Buxton-Bridges (Societal, TPP) Mogasale	Aballea FR (Societal, HCS) Aballea SP (Societal, TPP) Aballea Int'l, France (Societal, TPP) Maciosek Newall (Societal, HCS) Turner (Societal, HCS)
	-		• Aballea Int'l, Germany (Societal, TPP) • Aballea Int'l, Italy (Societal, TPP) • Nichol 2001 • Nichol 2003 • Lee

3.3.5.1 Societal Perspective

Ten studies presented an economic evaluation from the societal perspective for healthy working age adults. Aballéa published three different studies, each in a different geographic region of the world. One of Aballéa's studies was specific to France (Aballéa, Martin, Carrat, Drummond, & Weinstein, 2006) and one specific to Spain (Aballéa, et al., 2007), while the third study was applied to four different countries (France, Germany, Italy, Brazil) (Aballéa, et al., 2007). The Brazil analysis within the third study was not included due to the difference in health care setting to that of Canada. Aside from the Aballéa studies, the other economic evaluations were also geographically diverse, based in the United States, the United Kingdom, and Australia.

Of the ten studies, six performed CUAs and the remaining four were CBAs. The age groups in these studies varied. Some studies had a broad range from 18 to 64 years old and others a smaller age range from 18 to 50 years old. Others studies focused only on older working age adults, from 50 to 64 years old. The current policy in many countries is that only healthy adults over 65 years are provided publically funded influenza vaccine. The objective of studying the 50 to 64 year age group is to aid the decision of lowering the current age threshold from 65 years to 50 years old.

Starting with the 50 years and older group, Aballéa et al. published a series of CUAs with a diverse geographic span (France, Germany, Italy, and Spain). The studies had the same

intervention and comparator: vaccinating all adults from 50 to 64 years old compared to vaccinating only high risk adults 50 to 64 years old. Risk was defined as risk of complications due to influenza infection. The Aballéa studies used a decision analysis model and inputs were categorized as country-specific or non-country-specific. Country-specific inputs included population size, life expectancy, proportion of high risk individuals, current eligibility for vaccination, vaccination uptake under the current policy, influenza attack rate, national propensity to seek medical attention for ILI, probabilities of minor complications and hospital admission, and the case fatality rate of that particular country. Resource use and costs for vaccine, administration, physician visits, hospitalizations, outpatient treatment costs, and lost productivity were also considered country-specific. These data were generally taken from previous literature and country level administrative databases. Vaccine costs were €6.28 per unit with €20 GP administration fee or €2.90 occupational administration fee in France, €7 per unit for individuals eligible for public subsidization and €17.80 per unit for non-eligible individuals with a €6.50 GP administration fee in Germany, and €12.77 per unit at the pharmacy, €4.98 per unit through public health, with €8 administration fee from a physician in Italy. In Spain, vaccine price ranged from €13.49 to €17.97 per unit inclusive of administration, depending on workplace or physician administration and eligibility for subsidization. In the case that country-specific data were not available, the authors provided best possible estimates and determined whether other country data would be generalizable. If not, expert opinion was used. The location of vaccine administration was also adjusted by geographic location with some occurring in primary care settings and others with mixed specialist physician or occupational settings.

Non-country-specific inputs were assumed to be vaccine effectiveness, antiviral use, and lost work days. These inputs were generally taken from previous literature and systematic reviews. Vaccine effectiveness was determined from a previous Cochrane systematic review (Demicheli, Rivetti, Deeks, & Jefferson, 2004)and reduced incidence of ILI by 29%. Aballéa also assumed that this reduction was also applicable to physician visits, use of prescription medications, and lost workdays. Other effectiveness parameters were from previous studies and assumed to be 50% reduction in hospitalizations and 68% reduction in deaths; while these values appear to be high, the author states that these were estimated from a meta-analysis of 20 cohort studies. These studies however, were based on an elderly population and may overestimate the benefit of a vaccination across other younger populations. No adjustment to vaccine effectiveness was made for age. Utilities were derived from the Health Survey for England which surveyed participants using the EQ-5D. QALYs were calculated by applying weighting factors

representing the quality of life for each year of survival and summing over the number of years of life expectancy. Outcomes in the Aballéa study were cases of ILI, complications, deaths, lost work days and QALYs. Incidence of influenza infection was set to approximately 5% varying by country and age group.

The 2006 Aballéa study for France found that vaccinating all adults 50 to 64 years old compared to only high risk adults 50 to 64 years old had an incremental cost of €7,950 per QALY gained in 2003 Euros. The 2007 Aballéa study specific to Spain resulted in an ICER of €4,149 per QALY gained in 2004 Euros. The 2007 international Aballéa study that spanned several different countries had the following results in 2003 Euros: France had an incremental cost of €7,989 per QALY gained, and in Germany and Italy, the strategy was more effective, less costly, and hence dominant. Inputs for these countries differed, but the difference in results was driven mostly by vaccine uptake. In France, uptake in the current restrictive policy for high risk individuals is low while in Italy and Germany current vaccination uptake for high risk individuals is already relatively high. Changing to a less restrictive policy causes a greater increase in costs and also QALYs in France since a greater net number of high risk people would then access the vaccine compared to the increase in Italy or Germany. In Germany, the assumed overall increase in coverage, particularly among high risk people is less than that in the other countries, resulting in a correspondingly smaller gain in QALYs. Additionally, in Germany and Italy, the incremental societal cost of expanding vaccination is mitigated by the fact that under the current policy, individuals are already willing to purchase vaccine at prices much higher than contract prices. If a governmental program were to expand vaccination, it would be able to purchase vaccine at a lower contract price, effectively lowering the incremental cost of the program. This could influence the incremental costs for Italy and Germany compared to the incremental costs for France.

Maciosek et al., Newall et al., and Turner et al. also studied the 50 to 64 year old age group with decision models, as CUAs in the United States, Australia, and United Kingdom respectively (Maciosek, Solberg, Coffield, Edwards, & Goodman, 2006; Newall, Scuffhamd, Kelly, Harsley, & MacIntyre, 2008; Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006). The Newall study clearly reported a time horizon of one year; the others did not explicitly state a time horizon. Similar to Aballéa et al., the interventions in these three studies were vaccinating all adults 50 to 64 years old compared to only high risk adults 50 to 64 years old. Risk was defined as risk of complications due to influenza infection. Administration was assumed to be by a

primary care physician in the Turner study, 50% physician and 50% nurse in the Newall study, and not specified in the Maciosek study. Costs and model inputs were collected from various sources as described below.

In the Maciosek study, the authors undertook a systematic review of the literature to gather model inputs such as burden of disease figures, costs, resource use, and utility values. The study included costs for vaccine, administration, physician visits, hospitalizations, outpatient treatment costs, and lost productivity. Vaccine costs were $12.59USD per unit, physician visits were $198USD per visit, and hospitalizations were $7,276USD per visit. The outcomes in the Maciosek study were cases of ILI, death, and QALYs. Reduction in health resource use (hospitalizations due to pneumonia and influenza) was measured and used in the CBA as health outcomes were not monetized. Therefore, in the ICER equation only costs were accounted for in the numerator, and monetized benefits were not in the denominator of the ICER equation. Vaccine effectiveness was a reduced incidence of ILI of 18.9%. Other effectiveness parameters included a 36.6% reduction in hospitalizations and 42.9% reduction in mortality. Utilities were derived from the author's previous estimates without mention of method. The average utility reduction for non-hospitalized cases was approximated to be 0.30 for acute conditions and the duration of influenza episode was one week. Incidence of ILI was assumed to be approximately 15%.

The Newall study included costs for vaccine, administration, physician visits, hospitalizations, outpatient treatment costs, and lost productivity. These inputs were generally taken from databases. The study utilized the Australian Bettering the Evaluation And Care of Health database for GP costs as well as the Health Outcomes Information Statistical Toolkit database for hospitalizations and other medical resource use. Vaccine costs averaged to $17.47AUD per unit, physician visits were $38.68AUD per visit, and hospitalizations were $5,788AUD per visit for pneumonia and influenza infection, and $4,669 per visit for other respiratory conditions. Outcomes in the Newall study were cases of ILI, death, and QALYs. Reduction in cases of ILI was the measured outcome, which translated to a reduction in health resource use including hospitalizations. Vaccine effectiveness was determined from a previous Cochrane systematic review (Jefferson, Demicheli, Rivetti, Jones, Di, & Rivetti, 2006), with incidence of ILI reduced by 16% and preventing hospitalizations and deaths by 74% compared to no vaccination. Productivity losses from an infection were determined by applying an estimated loss of 2.6 days of work during the infection period of and multiplying by the average earnings per day of

$215AUD. Utilities were derived from a previous study which used the Assessment of Quality of Life survey among Australian participants (Hawthorne & Osborne, 2005). These utility weights were then applied to the estimated duration of illness to derive QALYs lost. Incidence of ILI was set to a relatively low rate of 1.9%.

The Turner study included costs for vaccine, administration, physician visits, hospitalizations, outpatient treatment such as over the counter medications, and lost productivity. These inputs were generally taken from previous literature or from the national Prescription and Pricing Authority Cost database. Vaccine costs averaged to £7.24 per unit, physician visits were £20.66 per visit, and hospitalizations were £2,656 per stay. Outcomes in the Turner study were cases of LCI and QALYs. Vaccine effectiveness was determined from a meta-analysis from the Cochrane library (Demicheli, Rivetti, Deeks, & Jefferson, 2004) and set to a 69% reduction in cases of LCI. Productivity losses were determined from a United Kingdom based earnings survey by multiplying the estimated loss of 2.9 days of work by the average earnings per day of £46.27. Utilities were derived from a previous antiviral study which recalibrated Likert scores to time-trade-off utilities. These utility weights were then applied to the estimated duration of illness to derive QALYs lost. Vaccine efficacy was set at 69% but was unspecific as to reductions in ILI, LCI, or other health outcomes. The attack rate of influenza was estimated at 6.55% obtained from the author's review of multiple randomized controlled studies examining prevention of influenza.

These three studies while different in geography and input values had only slightly different incremental costs. The Maciosek study reported an incremental cost of $28,044USD per QALY gained in 2000 United States dollars, the Newall study had an incremental cost of $8,338AUD per QALY gained in 2005 Australian dollars, and finally the Turner study resulted in an incremental cost of £10,766 per QALY gained in 2002 British pounds. The results from these three studies all fall into the same cost-effectiveness quadrant of improved effectiveness but increased costs for society.

Four studies investigated a broader age range of working age adults. The Buxton-Bridges study, Nichol 2001 and Nichol 2003 studies evaluated an age range of 18 to 64 years old. The Lee study pertained to 18 to 50 year old adults. All of these studies were performed as a CBA, took place in the USA, and were designed as either alongside a clinical trial or as a decision model. None of these studies monetized health outcomes and instead used lost productivity and health

resource use costs in the CBA. Time horizons were short with the Buxton-Bridges study at two flu seasons(Buxton-Bridges, et al., 2000) and the Lee study at one flu season(Lee, Matchar, Clements, Huber, Hamilton, & Peterson, 2002). Neither of the Nichol studies reported specific time horizons, but it can be inferred that a lifetime horizon was used as the studies accounted for the economic losses of a premature death (lifetime earnings) (Nichol, 2001; Nichol, Mallon, & Mendelman, 2003).

The location of the vaccine administration varied throughout the studies. The Buxton-Bridges study was performed at the Ford Motor Company in Michigan and vaccination occurred at the workplace. The Nichol studies assumed vaccination took place in medical clinics and the Lee study did not specify a location of administration.

The Buxton-Bridges study compared vaccinating all employees 18 to 64 years old at a car manufacturing plant to not vaccinating employees. This evaluation was performed alongside a randomized double-blind placebo controlled trial and model inputs were primarily based on the clinical trial. The CBA included costs for vaccine, administration, physician visits, hospitalizations, outpatient treatment costs, and lost productivity. For productivity costs, the author used the United States Bureau of Labor Statistics to estimate loss work days. Vaccine costs averaged $24.70USD per unit, physician visits were $34.39USD per visit, and hospitalizations were $7,790USD per stay.

This study was conducted over two flu seasons. As flu seasons vary in intensity, the study found variation in the results as well. Vaccine effectiveness was obtained directly from the clinical trial, where in the first flu season the vaccine did not match the circulating strain. In the 1997-98 season, the vaccine was ineffective and had a non-statistically significant 10% increase in cases of ILI versus placebo and a non-statistically significant 3% increase in cases of upper respiratory illness. This tallied to 45 more total workdays lost in the vaccinated group compared to the placebo group. The second flu season in which the vaccine matched the circulating strain, had a statistically significant 33% reduction in ILI and a non-statistically significant 13% reduction in upper respiratory illness, resulting in 32 workdays gained in the vaccinated group compared to placebo. Health outcomes such as reduction in ILI were monetized as the economic cost (the sum of lost productivity and work loss) of a clinical case of ILI using the human capital approach. No willingness-to-pay exercise was performed in this study. In both seasons, vaccination was not found to provide an economic benefit to society, with an incremental cost of

$65.59USD per employee in the 1997-98 season and $11.17USD per employee in the 1998-99 season.

Nichol 2001 was a CBA comparing vaccinating all healthy adults 18 to 64 years old to only vaccinating high risk adults 18 to 64 years old. Inputs such as influenza illness rates, hospitalizations, vaccine efficacy, and mortality rates were taken from previous literature and systematic reviews. Vaccination was modeled to be offered in various public locations such as workplace clinics, community health clinics, and public clinics in grocery and drug stores. Costs for vaccine, administration, physician visits, hospitalizations, and lost productivity were included. Vaccine costs were set at $10USD per unit, physician visits were $102USD per visit, and hospitalizations were $5,669USD per visit. In this study, productivity losses were a combination of actual absenteeism (work days lost) and workplace effectiveness at the place of work. The study assumed that influenza infection would reduce workplace effectiveness by 50% which would extend additional productivity losses, even if the individual had returned to work and was present at the workplace. No monetization of health outcomes other than accounting for lost productivity was included in this CBA. Vaccine effectiveness was determined as 66% reduction in LCI by factoring in the efficacy of a match between vaccine strain and circulating strain over several flu seasons, where a match implies strong but less than 100% protection.

The other Nichol study (2003) was designed in a very similar fashion, but the economic evaluation was done alongside a clinical trial in recruitment centres. The vaccine used was LAIV. Costs for vaccine, administration, physician visits, and lost productivity were included. Vaccine costs were unknown at the time of the study as this evaluation was designed to determine a breakeven price for the live, attenuated intranasal vaccine. Physician visits were $122USD per visit, and hospitalizations were not included in this trial. The author stated that studies conducted on LAIV had not statistically determined its effects on health care resource use and other outcomes, such as deaths. As a result, this economic evaluation only included resource use related to outpatient physician visits and productivity losses. No actual health outcomes (cases of ILI, case of LCI, deaths) were measured and only proxy health resource use measures and lost productivity measures were used in the analysis. Similar to the previous Nichol study, the author stated that clinical influenza illness or health outcome definitions may exclude or misclassify some important influenza-associated events, and accordingly, work loss, work at reduced effectiveness, and health care resource use were used to determine

effectiveness. Vaccine effectiveness was set as 18% reduction in work loss, 18% reduction in days of working at impaired effectiveness, and a 13% reduction in physician visits.
Both Nichol studies, found that vaccinating all healthy adults 18 to 64 years old was cost saving. In Nichol 2001, this net saving was $13.66USD per person vaccinated in 1998 United States dollars. The results of the Nichol 2003 study was a savings of $43.07USD per person vaccinated in 1997 United States dollars. While both were still cost saving, an important difference is that the Nichol 2003 study excluded hospitalizations. As stated before, in that study, Nichol et al. stated that hospitalizations were excluded because at the time of the economic evaluation, there were no studies to demonstrate the effect of LAIV on hospitalizations. However, this exclusion inherently causes a shift in the results. If hospitalizations were included, the results would change as vaccination would contribute to reductions in hospitalizations and improve the cost-benefit calculation. The appropriate approach for this study would have been an inclusion of hospitalizations and to monetize the benefit of averting hospitalizations, so cost-benefit calculations are thorough and complete.

Finally, the Lee study examined a broad range of adults 18 to 50 years old by conducting a CBA. Unfortunately, it did not specify the vaccine administration setting or the case definition of influenza. All model inputs and costs were based on previously published literature. The Lee study included costs for vaccine, administration, physician visits, and lost productivity. Vaccine costs were assumed to be $10.41USD per unit, physician visits were $27USD per visit, and hospitalizations were not included in this economic evaluation. The authors mentioned that no trial demonstrated vaccination decreasing hospitalization rates for influenza related illness. As for outcomes, this economic evaluation conducted a willingness to pay for influenza symptom relief analysis to determine the value of averting infections. These values, as well as lost productivity were used to determine the monetized value of the benefits of vaccination. Through a series of conjoint analyses from 210 patients, the Lee study determined that patients were willing to pay $15.49USD for a day of relief from influenza. Vaccine effectiveness was stated as a 68% reduction in influenza incidence. Productivity losses were accounted for as a loss of 2.8 work days, costing $142.10USD per day. Comparing the costs and benefits of vaccination of healthy adults to no vaccination resulted in a societal net benefit of $29.50USD per person in 2001 United States dollars.

3.3.5.2 Health Care System Perspective

Four studies took the health care system perspective and all performed CUAs. Geographically, the studies were based in the United Kingdom, France, and Australia, all countries that have publically funded health care systems. The time horizon for all of these studies was one year, with the exception of the Turner study, which did not explicitly report the time horizon used (Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006). However, it was inferred that a one year horizon was used.

All studies evaluated vaccinating all working age adults aged 50 to 64 years compared to the current policy of only vaccinating high risk adults aged 50 to 64 years. Risk was defined as risk of experiencing complications due to influenza infection.

The Mogasale study included costs for vaccine, administration, physician visits, and hospitalizations (Mogasale & Barendregt, 2011). All values were taken from governmental pricing indices such as the Pharmaceutical Benefits Scheme Schedule of Pharmaceutical Benefits for Approved Pharmacist and Medical Practitioners Index, National Hospital Cost Data Collection, MIMS Online Australia Database for treatment pricing. Vaccination was modeled to be offered during a physician visit. Vaccine costs were set at $11.88AUD per unit. Other unit costs were not shown in the study. Wastage was set at 3.5% of the total units and an additional 13.3% of the total units were “leaked” to those outside of the age group, also contributing to increased program cost. Incidence of circulating influenza was 1.79% and vaccine effectiveness was a 16% reduction in cases of influenza, 56% reduction in hospitalizations, and 33% reduction in deaths.

Details of the Aballéa study, Newall study, and Turner study were in the previous section. The Mogasale study was similar in many design aspects such as time horizon, outcomes, and population, but had some dissimilar inputs compared to the other studies.

The Mogasale study assumed a lower vaccination uptake on the standard high risk scenario and a higher uptake rate for the all adults scenario (Mogasale & Barendregt, 2011). This caused a greater incremental cost difference between the two programs relative to the other studies. Next, the efficacy of the influenza vaccine was lower in the Mogasale study compared to all of the other studies. For example, Mogasale et al. estimated the vaccine efficacy to be a 16% reduction in ILI, 56% reduction in hospitalizations, and 33% in deaths. These values are lower

than the Aballéa study which estimated a 29% reduction in ILI and a 68% reduction in deaths, and the Newall study which used a 74% reduction in hospitalizations and deaths. The Turner study differed in that it used LCI as an outcome measure and vaccine efficacy was set at 69% reduction in these cases. Incidence of influenza was also different in the Mogasale study at 1.79% while the other studies used varying estimates. Newall used a lower value of 0.93% and Aballéa and Turner set much higher probabilities of 4.69% and 6.55%, respectively.

With the exception of the Mogasale study, these economic evaluations found a similar directional result in that vaccinating all adults 50 to 64 years old would be effective but would also increase health care costs from the public health care system perspective. Aballéa et al. determined that from a French health care system perspective, the incremental cost was €13,010 per QALY gained, in 2003 Euros (Aballéa, Martin, Carrat, Drummond, & Weinstein, 2006). Turner reported an incremental cost of £6,174 per QALY gained, in 2002 British Pounds (Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006). Interestingly, the two economic evaluations conducted with the same population in Australia had different results. The Newall study uncovered that from the perspective of Australian Medicare, the incremental cost was $8,908AUD per QALY gained in 2005 Australian dollars (Newall, Scuffhamd, Kelly, Harsley, & MacIntyre, 2008). Measured in DALYs avoided, Mogasale et al. found a result that was considerably higher and less cost-effective with an ICER value of $111,574AUD per DALY avoided in 2003 Australian dollars. QALYs gained and DALYs avoided are conceptually similar but have differences in their methodology and assumptions; in this case the results from Newall et al. appear to be more cost-effective compared to the results of Mogasale et al. which are likely above most cost-effectiveness thresholds.

3.3.5.3 Third Party Payer Perspective

Three studies reported results from a third party payer perspective. Two of the three studies were CUAs conducted by Aballéa from two separate publications and were based in Spain, Italy, France, and Germany. The remaining study by Buxton-Bridges was a CBA conducted alongside a clinical trial based in the United States.

The population studied in the Aballéa study was a smaller subset of the adult population than the population studied by Buxton-Bridges et al. The Aballéa study focused on adults 50 to 64 years, while the Buxton-Bridges study included a broader age group of all adults aged 18 to 64 years. Buxton-Bridges et al. also used a longer time horizon of two years compared to the

Aballéa studies, which were for one year or one flu season (Buxton-Bridges, et al., 2000; Aballéa, et al., 2007). In the Aballéa study, costs and QALYs resulting from outcomes occurring during the intervention period were assessed over individuals' lifetimes, effectively capturing longer term outcomes. This meant that while the explicitly stated intervention time horizon was a single year, a second time horizon was used for outcomes as well.

From the Aballéa studies, the results in Western Europe were similar. In Spain, the ICER of providing vaccine to working age adults was €14,919 per QALY gained in 2004 Euros (Aballéa, et al., 2007). This result was very similar in France with an incremental cost of€13,156 per QALY gained (Aballéa, Martin, Carrat, Drummond, & Weinstein, 2006) and in Italy with an incremental cost of €15,652 per QALY gained(Aballéa, et al., 2007). However, Germany was an exception, with a much higher cost for third party payers resulting in an incremental cost of €31,387 per QALY gained in 2003 Euros. Country level differences such as vaccine effectiveness and uptake among these European countries affected the ICER calculation significantly. Compared to the societal perspective, these ICERs are higher for all countries, shifting the cost-effectiveness quadrant for Italy and Germany from a dominant result to one of higher cost and greater effectiveness from the third party payer perspective.

Buxton-Bridges et al. illustrated that similar to the societal perspective, providing all adults 18 to 64 years with influenza vaccine is not cost-effective from the third party payer perspective (Buxton-Bridges, et al., 2000). Over the two flu seasons examined, there was a net loss of $7.66USD per person vaccinated in the 1998-99 year and a net loss of $24.41USD per person vaccinated in the 1997-98 year. Of note, these two influenza seasons were mild in comparison to other years as reported by the authors and the vaccine mismatch in the first flu season significantly reduced its efficacy.

Table 25: Data Extraction for Healthy Working Adults

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Cost Items	Health Outcomes
Aballéa (France, Societal), 2006	Healthy adults, 50 - 64 years	Societal	CUA	France	1 year	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, co-payments, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments, absenteeism	Cases of ILI, complications, hospitalizations, death
Aballéa (Spain, Societal), 2007	Healthy adults, 50 - 64 years	Societal	CUA	Spain	1 year	EUR, 2004, no need for discounting	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, co-payments, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments, absenteeism	Cases of ILI, complications, hospitalizations, death
Abelléa (France, Societal), 2007	Healthy adults, 50 - 64 years	Societal	CUA	France	Single flu season	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, co-payments, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments, absenteeism	Cases of ILI, complications, hospitalizations, death
Abelléa (Germany, Societal), 2007	Healthy adults, 50 - 64 years	Societal	CUA	Germany	Single flu season	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, co-payments, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments, absenteeism	Cases of ILI, complications, hospitalizations, death
Abelléa (Italy, Societal), 2007	Healthy adults, 50 - 64 years	Societal	CUA	Italy	Single flu season	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, co-payments, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments, absenteeism	Cases of ILI, complications, hospitalizations, death
Buxton-Bridges (Societal), 2000	Healthy adults, 18 - 64 years	Societal	CBA	USA	Two flu seasons	$USD, 1998/99, no mention	Alongside RCT	Vaccination	No vaccination (placebo)	Vaccine, administration, co-payment, physician visits, hospitalization, treatment/drugs, lost work day	Cases of ILI and URI

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 25: Data Extraction for Healthy Working Adults, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Costs	Health Outcomes
Lee, 2002	Healthy adults, 18 - 50 years	Societal	CBA	USA	Single flu season	$USD, 2001, no mention	Decision Model	Vaccination	No vaccination	Vaccine, administration, physician visits, treatment/drugs, lost work days	Unspecified influenza infection
Maciosek, 2006	Healthy adults, 50 - 64 years	Societal	CUA	USA	Not reported	$USD, 2000, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration physician visits, hospitalization, treatment/drugs, patient time, travel costs	Cases of ILI, hospitalizations, deaths
Newall (Societal), 2008	Healthy adults, 50 - 64 years	Societal	CUA	Australia	1 year	$AUD, 2005, 5%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visits, hospitalization, diagnostic tests, lost work days	Cases of ILI, hospitalizations, deaths
Nichol, 2001	Healthy adults, 18 - 64 years	Societal	CBA	USA	Not reported	$USD, 1998, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visits, hospitalizations, treatment/drugs, absenteeism, work effectiveness	Cases of LCI, work absenteeism, work effectiveness days, physician visits, hospitalizations, deaths
Nichol, 2003	Healthy adults, 18 - 64 years	Societal	CBA	USA	Not reported	$USD, 1997, no mention	Alongside RCT	Vaccination for all adults LAIV	Vaccination for high risk adults only	Vaccine, administration, physician visits, hospitalizations, treatment/drugs, absenteeism, work effectiveness	Days of work missed, days working at reduced effectiveness, days with a health care provider
Turner (Societal), 2006	Healthy adults, 50 - 64 years	Societal	CUA	United Kingdom	Not reported	£, 2002, no mention	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration Physician visit, hospitalization, treatment/drugs, absenteeism, travel costs	Cases of LCI, QALYs

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 25: Data Extraction for Healthy Working Adults, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Vaccination Costs Medical Costs Productivity Costs	Health Outcomes
Aballéa (France, HCS), 2006	Healthy adults, 50 - 64 years	Health Care System	CUA	France	1 year	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visit, hospitalization, treatment/drugs, diagnostic tests	Cases of ILI, complications, hospitalizations, death
Mogasale, 2011	Healthy adults, 50 - 64 years	Health Care System	CUA	Australia	1 year	$AUD, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visits, hospitalization, treatment/drugs	ILI incidence, hospitalizations, deaths
Newall (HCS), 2008	Healthy adults, 50 - 64 years	Health Care System	CUA	Australia	1 year	$AUD, 2005, 5%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visits, hospitalization, diagnostic tests	Cases of ILI, hospitalizations, deaths
Turner (HCS), 2006	Healthy adults, 50 - 64 years	Health Care System	CUA	United Kingdom	Not reported	£, 2002, no mention	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visit, hospitalization, treatment/drugs	Cases of LCI, QALYs

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 25: Data Extraction for Healthy Working Adults, Continued

Author, Year	Relevant Target Population	Perspective	Analytical Technique	Country	Time Horizon	Currency, Costing Year, and Discounting	Model Type	Intervention	Comparator (Standard of Care)	Costs	Health Outcomes
Aballéa (Spain, TPP), 2007	Healthy adults, 50 - 64 years	Third Party Payer	CUA	Spain	1 year	EUR, 2004, no need for discounting	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments	Cases of ILI, complications, hospitalizations, death
Abelléa (France, TPP), 2007	Healthy adults, 50 - 64 years	Third Party Payer	CUA	France	1 year	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments	Cases of ILI, complications, hospitalizations, death
Abelléa (Germany, TPP), 2007	Healthy adults, 50 - 64 years	Third Party Payer	CUA	Germany	Single flu season	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments	Cases of ILI, complications, hospitalizations, death
Abelléa (Italy, TPP), 2007	Healthy adults, 50 - 64 years	Third Party Payer	CUA	Italy	Single flu season	EUR, 2003, 3%	Decision Model	Vaccination for all adults	Vaccination for high risk adults only	Vaccine, administration, physician visit, hospitalization, treatment/drugs, diagnostic tests, sick leave payments	Cases of ILI, complications, hospitalizations, death
Buxton-Bridges (TPP), 2000	Healthy adults, 18 - 64 years	Third Party Payer	CBA	USA	Two flu seasons	$USD, 1998/99, no mention	Alongside RCT	Vaccination	No vaccination (placebo)	Vaccine, administration, physician visits, hospitalization, treatment/drugs	Cases of ILI and URI

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; URI = upper respiratory illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros; TPP = third party payer

Table 26: Results for Healthy Working Adults

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Aballéa (France, Societal), 2006	€42.10M for cohort of 500000 adults	-116659 influenza cases, -5335 hospitalizations, -436 deaths, -142852 absent days, 8036 years of life, 5036 QALYs	€7950/QALY	$15525CAD/QALY
Aballéa (Spain, Societal), 2007	€10.2M for Spanish population	-70638 ILI cases, -2908 hospitalizations, -209 deaths, -106438 lost workdays, 2469 QALYs	€4149/ QALY	$7855CAD/QALY
Abelléa (France, Societal), 2007	€43.0M for French population	5379 (1182 - 12801) QALYs for French population	€7989/QALY	$15600CAD/QALY
Abelléa (Germany, Societal), 2007	-€14.93M for German population	1636 (310 - 3805) QALYs for German population	Dominant	Dominant
Abelléa (Italy, Societal), 2007	-€1.79M for Italian population	2812 (598 - 6691) QALYs for Italian population	Dominant	Dominant
Buxton-Bridges (Societal), 2000	1997/98 season: $65.59 loss/person, 1998/99 season: $11.17 gain/person	1997/98 season: 33 ILI cases, 27 URI cases. 1998/99 season: -40 ILI cases, -19 URI cases	98/99 year: $65.59 loss/person vaccinated. 97/98 year: $11.17 loss/person vaccinated	98/99 year: $123.42CAD loss/person vaccinated. 97/98 year: $20.61CAD loss/person vaccinated
Lee, 2002	$29.50 USD per recipient	68% reduction in infection	$29.50 USD per recipient, net benefit	$54.16 CAD per recipient, net benefit
Maciosek, 2006	$1.53B for cohort of 4M	1296889 ILI cases prevented, 16583 hospitalizations prevented, 2851 deaths prevented, 54415 QALYs gained	$28044/QALY gained	$50997CAD/QALY
Newall (Societal), 2008	$6.72/ person or $23.7M for population of 3.5M	0.0003QALYs/person or 1058 QALYs for population of 3.5M	$2824/ILI averted, $7527/hospitalization averted, $98602/death averted, $8338/QALY	$2649CAD/ILI averted, $7991CAD/hospitalization averted, $104680CAD/death averted, $8851CAD/QALY
Nichol, 2001	$13.66 saved/person	-5.5 cases/100 persons, (3.2-9.0), -12.3 days/100 persons (4.7-25.2), -3.8/ days100 persons (2.1-6.6), -2.5 visits/100 persons (1.2-4.5), -2.6 hospitlns/10000 persons (1.1-4.3), -0.77 deaths/100000 persons (0.40 - 1.2)	breakeven $13.66/person vaccinated	breakeven $25.70CAD/person vaccinated

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros

Table 26: Results for Healthy Working Adults, Continued

	Difference in Costs	Difference in Effect	Results (base case)	Results in 2013 CAD (base case)
Nichol, 2003	$43.07/person	Relative rate 0.82 (0.74 - 0.91), 0.82 (0.74-0.91), 0.87 (0.77 - 0.98)	breakeven $43.07/person vaccinated	breakeven $79.47CAD/person vaccinated
Turner (Societal), 2006	£485849/100000 individuals	106 (43, 207)	£253/LCI case, £10766/QALY	$30022CAD/QALY
Aballéa (France, HCS), 2006	€68.89M for cohort of 500000 adults	-116659 influenza cases, -5335 hospitalizations, -436 deaths, -142852 absent days, 8036 years of life, 5036 QALYs	€13010/QALY	$25407CAD/QALY
Mogasale, 2011	$43.4M for population of 3.3M	-5150 ILI cases, -313 hospitlns, -30 deaths, 620 life years lost, 366 DALYs lost	$8421/ILI case averted , $138465/hospitalization averted, $1436501/death averted, $111574/DALY	$116435CAD/DALY
Newall (HCS), 2008	$2.67/ person or $9.4M for population of 3.5M	0.0003QALYs/person or 1058 QALYs for population of 3.5M	$3017/ILI averted, $8041/hospitalization averted, $105343/death averted, $8908/QALY	$3202CAD/ILI averted, $8536CAD/hospitalization averted, $111837CAD/death averted, $9456CAD/QALY
Turner (HCS), 2006	£653221/100000 individuals	106 (43, 207)	£145/LCI case, £6174/QALY	$17217CAD/QALY
Aballéa (Spain, TPP), 2007	€36.8M for Spanish population	-70638 ILI cases, -2908 hospitalizations, -209 deaths, -106438 lost workdays, 2469 QALYs	€14919/ QALY	$28246CAD/QALY
Abelléa (France, TPP), 2007	€70.8M for French population	5379 (1182 - 12801) QALYs for French population	€13156/QALY	$25691CAD/QALY
Abelléa (Germany, TPP), 2007	€46.73M for German population	1636 (310 - 3805) QALYs for German population	€31387/QALY	$61294CAD/QALY
Abelléa (Italy, TPP), 2007	€44.02M for Italian population	2812 (598 - 6691) QALYs for Italian population	€15652/QALY	$30565CAD/QALY
Buxton-Bridges (TPP), 2000	1997/98 season: $24.41 loss/person, 1998/99 season: $7.66 loss/person	1997/98 season: 33 ILI cases, 27 URI cases. 1998/99 season: -40 ILI cases, -19 URI cases	98/99 year: $7.66 loss/person vaccinated. 97/98 year: $24.41 loss/person vaccinated	98/99 year: $14.03CAD loss/person vaccinated. 97/98 year: $45.04CAD loss/person vaccinated

CUA = cost-utility analysis; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; QALYs = quality-adjusted life years; DALYs = disability adjusted life years; LCI = laboratory-confirmed influenza; ILI = influenza-like illness; AOM = acute otitis media; USD = US dollars; CAD= Canadian dollars; EUR = Euros; TPP = third party payer; HCS = health care system

3.4 Provincial Policy Results

The second objective of the thesis was to compare and contrast the various influenza immunization policies across Canada.

From the scan of provincial websites, six provinces (Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, Newfoundland) and three Canadian territories (Nunavut, Yukon Territory, Northwest Territories) offer universal influenza immunization programs as of 2015. The details of each province's program are listed below in Table 27. In Prince Edward Island, a unique "universal" program exists, in which the cost of the vaccine is publically funded but the administration cost of the vaccine is charged for certain groups while others are exempt from paying the administration fee. In 2014, the administration fee was set at $7CAD (Government of Prince Edward Island, 2014).

Three provinces (British Columbia, Quebec, New Brunswick) provide a targeted influenza immunization program. In these provinces, only high risk groups are provided publically funded vaccine. Those not in high risk groups can receive vaccine through out-of-pocket payment.

Table 28 shows a national summary table breaking down coverage by province and by risk type. This table reveals that influenza vaccination policies vary among provinces that have targeted programs. For instance, children 6 to 59 months of age are provided publically funded influenza vaccine in British Columbia, but children 24 months to 59 months did not fall into the high risk category in Quebec. Several more differences emerged among the provinces. Aboriginal peoples were deemed high risk in British Columbia but in Quebec, it was stated that only those in remote or isolated communities qualified. In New Brunswick, persons on long-term use of acetylsalicylic acid are provided publically funding for vaccination, but in British Columbia this group of individuals is excluded.

Differences in coverage exist for working age adults, depending on their occupational risk of exposure. All provinces in Canada provide publically funded vaccine to health care workers. However, first responders, defined as police and correctional officers, firefighters, and ambulance workers and paramedics who provide essential community services, were specifically identified in British Columbia. Quebec and New Brunswick do not specifically identify this group under public funding.

Table 27: Additional Provincial Details Regarding Influenza Immunization Policy

	Universal	Targeted	Immunization Program Policy Details
BC		**X**	Vaccine is provided free to people at high risk of serious illness from influenza or able to transmit or spread influenza to those at high risk of serious illness from influenza (BC Centre for Disease Control, 2014)
AB	**X**		Vaccine is free at any of the Alberta Health Services influenza immunization clinics. (Alberta Health Services, 2014)
SK	**X**		Every Saskatchewan resident is eligible to receive free seasonal influenza immunization. (Government of Saskatchewan)
MB	**X**		Annual seasonal flu shot is available to all Manitobans at no charge from family doctors and public health nurses. (Government of Manitoba, 2014)
ON	**X**		All Ontarians aged 6 months or older, may receive the publicly-funded influenza vaccine through the Universal Influenza Immunization Program (UIIP). (Ministry of Health and Long Term Care)
QC		**X**	Vaccination is free for people at higher risk of developing complications either due to their age or health. (Sante et Services Sociaux Quebec, 2014)
NS	**X**		Vaccine is free for all Nova Scotians. (Government of Nova Scotia)
NB		**X**	Publicly funded influenza vaccine available for individuals at high risk of influenza complications as well as for members of their households. (Government of New Brunswick, 2015)
PE	**X***		Vaccination is free for seniors age 65 and over, children aged 6 - 59 months, pregnant women and household contacts of pregnant women. *A $7 administration fee is charged to all others wishing to be vaccinated (Prince Edward Island Department of Health and Wellness, 2014)
NL	**X**		The Newfoundland and Labrador immunization schedule recommends and provides influenza vaccine for all persons and in particular for those who are at increased risk for complications from influenza. (Government of Newfoundland and Labrador, 2015)
YT	**X**		Vaccine is available to all Yukoners (Government of Yukon)
NT	**X**		Universal immunization program in the NWT offered annually free of charge (Northwest Territories Health and Social Services, 2015)
NU	**X**		Nunavut has a universal influenza immunization program. (Nunavut Department of Health)

Even within a specific risk group, provinces with targeted programs had differing policies. For instance, in British Columbia, pregnant women are only considered high risk when they enter their third trimester and would deliver during the influenza season. Women in their first or second trimester would not be able to receive publically funded influenza vaccination. However, in New Brunswick, all pregnant women, regardless of which trimester they are in, are considered high risk and could access publically funded vaccine.

Differences even occur among universal immunization programs. In Ontario, Alberta, and Northwest Territories, the universal immunization program is simply promoted to all residents across all ages and groups. However, this is not the case in the other provinces and territories with universal programs. In Yukon, Saskatchewan, Manitoba, Nova Scotia, and Newfoundland, while a universal immunization program is in place, public health promotions are geared to high risk groups only.

Table 28: Differentiation of Provincial Policies by Universality and Risk Groups

Risk Groups	BC	AB	SK	MB	ON	QC	NB	NS	PE	NL	NT	YK	NU
Universal vaccination	N	Y[3]	Y[2]	Y[5]	Y[3]	N	N	Y[2]	Y[6]	Y[2]	Y[4]	Y[2]	Y[4]
Persons with morbid obesity (BMI ≥ 40)	Y	Universal – all residents are provided vaccine	Universal – all residents are provided vaccine	Universal – all residents are provided vaccine	Universal – all residents are provided vaccine	Y	Y	Universal – all residents are provided vaccine	P	Universal – all residents are provided vaccine	Universal – all residents are provided vaccine	Universal – all residents are provided vaccine	Universal – all residents are provided vaccine
Aboriginal peoples	Y					Y[7]	Y		P				
Healthy children 6 to 59 months of age	Y					N	Y		Y				
Pregnant women in their 3rd trimester, expecting to deliver in influenza season	Y					Y[8]	Y		Y				
Pregnant women, any trimester	N					Y[9]	Y		Y				
Children 6 months to 23 months	Y					Y	Y		Y				
Persons 18 years and older	N					N	N		P				
Persons 50-64 years	N					N	N		P				
Persons 60 years and older	N					Y	N		P				
Persons 65 years and older	Y					N	Y		Y				
Residents of nursing homes or chronic care facilities	Y					Y	Y		Y				
Health care workers	Y					Y	Y		Y				
Children and adolescents on long-term ASA	Y					Y	Y		P				
Persons on long-term ASA (e.g. RA patients)	N					Y[10]	Y		P				
Household contacts of people at high-risk	Y					Y	Y		P				
Persons with weakened immune systems	Y					Y	Y		P				
Essential community services: first responders	Y[1]					N	N		P				
Persons at risk travelling to destinations where influenza is likely circulating	N					Y[11]	N		P				
Persons in direct contact with poultry infected with avian influenza during culling operations	Y					Y	N		P				

1. Police, firefighters, ambulance personnel, and correctional officers.
2. The flu vaccine is available free of charge to all residents; however, public education campaigns focus attention on immunizing high risk groups.
3. Vaccine is available free of charge to individuals aged 6 months or older who live, work or attend school in Alberta/Ontario.
4. Vaccine is free of charge to anyone who requests it.
5. The vaccine is available free of charge to all Manitoba residents aged 6 months or older; however, public education campaigns focus attention on immunizing high risk groups.
6. Vaccine is free of charge to all residents of PEI; however, administration of the vaccine is not covered except for those noted in the table.
7. People living in remote or isolated communities.
8. The influenza vaccine is given to all women who are in their second or third trimester (13 weeks or more).
9. Only when the pregnant woman has a medical condition that puts them at high risk of complications.
10. For people aged 18 and up
11. Free for people with an underlying condition. Recommended but not free for people otherwise in good health

Y = fully funded; N = not funded; P = partly funded

Table 28: Differentiation of Provincial Policies by Universality and Risk Groups, Continued

Adults and children with chronic conditions severe enough to require regular medical follow-up or hospital care	BC	AB	SK	MB	ON	QC	NB	NS	PE	NL	NT	YK	NU
Cardiac disease	Y	All Chronic Care Patients	All Chronic Care Patients	All Chronic Care Patients	All Chronic Care Patients	Y	Y	All Chronic Care Patients	P	All Chronic Care Patients	All Chronic Care Patients	All Chronic Care Patients	All Chronic Care Patients
Pulmonary disease	Y					Y	Y		P				
Asthma	Y					Y	Y		P				
Diabetes	Y					Y	Y		P				
Renal disease	Y					Y	Y		P				
Liver disease	Y					Y	Y		P				
Anaemia or hemoglobinopathy	Y					Y	Y		P				
HIV patients	Y					Y	Y		P				

(Public Health Agency of Canada, Canadian Nurses Coalition on Immunization, Canadian Pharmacists Association, 2015)

4 DISCUSSION

Of 35.2 million people in Canada, 22 million (62%) Canadians live in a province with universal access to a publically funded influenza immunization program (Statistics Canada, 2015). While this is a considerable number of people, there are questions about the discrepancies in policy across provinces and any potential impact provincial discrepancies may have. In certain provinces, the absence of a universal influenza immunization program may discourage uptake rates, create barriers for immunization, and potentially affect overall population immunity. It is important therefore to identify and review the literature to determine whether universally providing influenza vaccine across all provinces is a potentially viable and cost-effective public health intervention.

This section will discuss the quantity and quality of the literature with respect to cost effectiveness as determined in this review, best methods and practices from this thesis, and provide suggestions for influenza immunization policy. Additionally, other aspects of immunization policy will be discussed including pandemic influenza and mandatory vaccination policies.

4.1 Summary of Major Findings

4.1.1 Design and Quality of literature

This thesis identified 41 eligible economic evaluations examining the cost-effectiveness of influenza immunization programs. Of these, 31 economic evaluations were deemed acceptable quality or high quality. The primary reasons for poorer quality were lack of refined definitions of populations, vaccine efficacy, health outcomes, or perspective taken in the analysis. Some studies also did not provide a full incremental economic evaluation and did not provide a full description of the comparator while other studies were not transparent on the definition of "coverage"—as a description of vaccine uptake, or a description of the funding of the vaccine. Clarity on sources and key definitions were the main driver of lower quality.

Certain population subgroups that reflect different degrees of risk and cost-effectiveness emerged from the literature: children and adolescents, pregnant and postpartum women, healthy working adults, and high risk patients. It is encouraging to have 31 acceptable quality or high quality studies on the topic of the health economics of seasonal influenza immunization programs. This implies research interest in seasonal influenza immunization programs and their

cost effectiveness. The results from these studies are insightful in providing suggestions for future policy decisions. The economic evaluations included were conducted from the societal, public health payer, and third party health payer perspectives, generally considered appropriate and useful for policy makers. Within this thesis to further ensure that the literature brought forward was of relevance and high quality, a best-evidence synthesis was conducted, with set inclusion and exclusion criteria specific to the research objectives. There is an abundance of literature on this topic and setting specific criteria ensured that included studies were relevant in addressing the research questions. For instance, though there is a vast amount of literature studying antiviral treatment, this review was focused on influenza immunization. Similarly, a large amount of research has been conducted on pandemic influenza, which is managed differently than seasonal influenza. Pandemic influenza requires the use of more drastic policy measures including the possible use of antivirals for primary prevention and social distancing methods, such as isolating suspected infected individuals. While these topics were not the focus of the thesis, antiviral treatment and pandemic influenza are important aspects of managing influenza and their relevance are addressed later in this section and in the future research section.

Besides relevance, another component of the best-evidence synthesis is quality. Assessing quality was extremely important in this thesis and using the combination of the SIGN checklist with the vaccine specific questions adapted from WHO economic evaluation of immunization programs guidelines allowed for an effective and comprehensive quality appraisal. The SIGN checklist, while a validated and useful quality appraisal tool, is not specific to immunization programs. The addition of the WHO immunization questions complemented the SIGN checklist with a vaccine perspective. Questions regarding vaccine administration, wastage, and herd immunity are important parameters and should be considered in these economic evaluations.

Both quality appraisal tools were comprised of closed-ended “yes,” “no,” or “not applicable” type questions and did not use a numerical scoring system (Scottish Intercollegiate Guidelines Network, 2015; Initiative for Vaccine Research, 2008). This made quality appraisal straight-forward, effective, and efficient with the SIGN checklist providing10 questions, and the adapted WHO economic evaluation checklist providing an additional five questions. A simple answer “yes, no, or not applicable” scheme allowed for a clearer quality delineation among the studies. A scoring questionnaire also could be beneficial in that it may be able to quantify parameters of quality in numerical detail. However, for the purposes of this thesis, assigning thresholds for low

and high quality, creating numerical definitions of “acceptable” or “unacceptable,” and quantifying quality was found to be complex and subjective. Scoring domains and associated thresholds may appear arbitrary and total scores may not be fully representative of a study’s quality. For example, if a total score of one study was 30 points and another 27 points, it could be misinterpreted that the first study is “ten percent better” than the second study. The total scores for these two studies also may not provide the reader enough detail on *how* they were scored. In this example, the first study, though it has a greater numerical score, may have high quality across several domains, but also possess unacceptable quality in other scoring domains. On the other hand, the second study may have a lower total score, but has scores evenly balanced across all domains. Such scoring issues do not arise with a closed-ended “yes, no, not applicable” checklist and so it was decided that using the aforementioned checklists would be appropriate for this thesis. Conversely, there certainly also are limitations of a non-scored questionnaire. By only providing closed ended answers to a checklist, there is the potential of overly rough categorizations of the quality of the studies. A scored checklist can provide a more refined level of detail that a non-scored questionnaire cannot demonstrate. In reality, not all quality parameters can simply be assigned a “yes, no, not applicable” answer. Numerical scoring shows more subtle differences among the quality of studies. Practically speaking, the decision to use one quality appraisal tool over another is subject to the topic and the purpose of the appraisal. For the purposes of this thesis, the tools were appropriate to the task at hand. In addition to recognizing the strengths and limitations of each type of checklist, the SIGN checklist came with clear guidelines to assist with answering each question in a simple manner. These guidelines helped with the appraisal and further assisted and ensured a balance of efficiency, simplicity, and utility.

While the quality of the included studies was strong overall, there were some significant weaknesses that the appraisal revealed. The lack of a justified study design was a common deficiency in the current literature on influenza immunization programs. Authors rarely discussed the rationale for the selected design. Instead, more effort was put to describing the design itself. Given that differences in design often lead to differences in results, it would have been helpful for authors to have stated the rationale for one study design over another to allow readers to better interpret study results.

Another interesting finding from the quality appraisal was with regards to discounting and time horizon. The vast majority of studies did not include discounting in their analyses, appropriate

given the relatively short durations of the economic evaluations. Time horizons shorter than one year do not require discounting and in the case of influenza seasons, which typically last in the range of 3 to 6 months, discounting can be appropriately disregarded. Most studies had explicitly stated short time horizons in the range of a single flu season or a year. These stated time horizons were generally for the intervention (i.e. vaccination). Implicitly however, studies that accounted for life years or QALYs lost also had used a second longer time horizon, often set to individuals' lifetimes. With an acute infection of influenza, there is a small but material potential that some health outcomes may occur after a longer period of time. For instance, the negative effects of pneumonia secondary to an influenza infection could persist many months after the initial infection. Essentially, the literature often states a short time horizon based on the length of a flu season, but depending on the study, there may actually and inherently be longer time horizons within the analysis. For these included economic evaluations and others examining infectious diseases like influenza, two time horizons exist: one for the intervention, and another time horizon at the individual level which accounts for the longer term outcomes, such as life years lost. Studies could have been more precise about time horizons, or alternatively, could have conducted explicit sensitivity analyses with different time horizons.

Two studies which specifically and explicitly stated rationale for a longer time horizon for longer term outcomes were the Sander study and the Clements study which had time horizons set to the lifetime of the individual level (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011; Sander, et al., 2010). Future economic evaluations can benefit from incorporating the features that were in the Clements and Sander studies. Alternatively, future studies could also look to the Pitman study which incorporated a very long time horizon of 200 years to allow for discounted costs and benefits to fully accrue (Pitman, Nagy, & Sculpher, 2013). This time horizon was explicitly described and necessitated as part of the dynamic transmission model used in the analysis.

While not the time horizon of a study, another important element of the studies linked to timing is the actual year or flu season modeled for the analysis. Given that the circulating influenza strain generally differs over time, the year or season modeled may affect certain model parameters such as vaccine efficacy. In many of the economic evaluations this is managed by using an average efficacy across multiple seasons, but in cases where an economic evaluation was conducted alongside an efficacy trial (which may only be conducted for a single year or season), it is important to recognize that differences in circulating strain and vaccine match can

influence the results considerably. This was demonstrated in the Buxton-Bridges study, where vaccine efficacy in one year was low due to a mismatch, but was higher in the following year (Buxton-Bridges, et al., 2000).

When it comes to the analytic technique performed, thirteen of the 31 studies conducted a CBA, but yet the monetization of outcomes was only present in two of the thirteen CBAs. Both the Salleras study and the Lee study performed a willingness-to-pay exercise to determine the monetary value of health outcomes. In the Lee study it was found participants were willing to pay $16USD for a day of symptom relief; in the Salleras study parents were willing to pay €20 to avoid a lost school day for their children and €40 for a lost work day (Lee, Matchar, Clements, Huber, Hamilton, & Peterson, 2002; Salleras, et al., 2009).However, the other eleven CBAs did not perform any monetization of the health outcome but instead only factored in lost time and productivity into the analysis. This is an important point about the quality of the CBAs, as the technical definition of a true CBA requires the valuation and monetization of health outcomes. For these studies, while calculating lost productivity is acceptable to determine the value of averting an influenza infection, it would not be unreasonable to expect for these CBAs to have also incorporated a valuation of the *monetary value* of health outcomes similar to Salleras et al. and Lee et al.

Aside from this, across all studies an essential part of immunization and its economic evaluations is with regards to herd immunity. The question on herd immunity was an important vaccine related quality appraisal question and yet, many studies generally dismissed or did not explicitly include it in the analysis. Some studies explicitly included herd immunity into the model or performed a separate sensitivity analysis to test the effects of herd immunity on results. Examples include the Pitman and Clements studies; in the Pitman study, the effect of herd immunity was included in the dynamic transmission model (Pitman, Nagy, & Sculpher, 2013). In the Clements study, herd immunity was in a separate sensitivity analysis where an additional reduction in cases of ILI was modeled (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011).There were other studies that explicitly adjusted for herd immunity in the model by adding a certain value to the vaccine efficacy estimate, such as the Jit study where some protection was afforded from mother to neonatal child (Jit, Cromer, Baguelin, Stowe, Andrews, & Miller, 2010).

However, most of the studies were not specific with regard to herd immunity. Studies that relied on efficacy estimates from clinical trials or crude reductions in influenza incidence are more likely to have missed incorporating herd immunity. This is a point that needs improvement in future studies since herd immunity is an essential input for economic evaluations of immunization programs. Often the effects of herd immunity or indirect protection contribute (either positively or negatively) to the cost-effectiveness of vaccination. Without capturing the effects of indirect protection, a potentially major component of vaccination is lost and cost-effectiveness may be improperly estimated. And while herd immunity is generally thought of as a benefit, in some cases for other infectious diseases, herd immunity estimations may actually shift the average age of infection for individuals to be later in life and cause downstream infections in older individuals with a greater risk of complications. Brisson and Edmunds describe that susceptible individuals are less likely to come into contact with infectious individuals because of herd immunity, and therefore these susceptible individuals tend to be older if they become infected (Brisson & Edmunds, 2003). For some diseases such as varicella (chicken pox), the viral infection can often be more severe for older individuals therefore resulting in a greater negative outcome and a resultant overestimated benefit of herd immunity (Brisson & Edmunds, 2003). However, these conclusions regarding herd immunity for varicella may not be completely applicable to a disease like influenza. Unlike varicella, influenza is seasonal, emerging and circulating on an annual basis. Influenza could infect individuals several times over an entire lifetime. In any case, from the literature it appears that herd immunity effects for influenza could be better captured in models or sensitivity analysis, or at least, clearly mentioned and addressed, in future economic evaluations of influenza immunization programs.

When considering more logistical considerations of vaccination, the studies were generally descriptive and clear about the administration of the vaccine. Since administration of the vaccine shapes the processes, scale, setting, and cost of an immunization program, it is essential for studies to properly detail it. However, one major pragmatic aspect of immunization programs not incorporated into many of the studies was the issue of vaccine wastage. Virtually every study, with the exception of the Jit study, Maciosek study, Mogasale study, and Newall study, did not factor any wastage in the evaluation(Jit, Cromer, Baguelin, Stowe, Andrews, & Miller, 2010; Maciosek, Solberg, Coffield, Edwards, & Goodman, 2006; Mogasale & Barendregt, 2011; Newall, Scuffhamd, Kelly, Harsley, & MacIntyre, 2008). Vaccine wastage stems from an under-utilization and over-purchase of vaccine—ultimately a mismatch of supply and demand. Ensuring an adequate supply and avoiding potential wastage of vaccine is important to both

public health agency funders and vaccine manufacturers. From the pragmatic sense, purchasing more vaccine than is necessary results in wastage as vaccines have limited shelf life and generally expire shortly after the influenza season. For manufacturers, fulfilling the vaccine orders and requirements for one consumer can result in shortages for another consumer. Vaccine production requires lead time and manufacturing capacity, so if one customer is demanding high quantities of vaccine, this may mean that another customer will be in the queue for the next available production batch. Ultimately, improper vaccine forecasting can cause significant problems and directly influence the successful operations of a program, and it was found that many of the studies included did not adequately factor this into the analyses.

Beyond these logistical aspects of the studies, there also needs to be a high level of external validity to the studies to be used for decision making. The generalizability of studies is dependent on several factors, such as the demographics and the epidemiology of the condition in the population studied, the health care resources consumed and variations in clinical practice, and pricing and the local costs of goods and services. These could vary between the study and the jurisdiction a policy maker is interested in. Within this thesis, certain studies have more applicability to the Canadian health care environment. To start, the Skedgel study and the Sander study, both based in Canada, are likely more applicable to Canadian decision makers given the relative similarity in health care environments across provinces(Skedgel, Langley, MacDonald, Scott, & McNeil, 2011; Sander, et al., 2010). These studies were modeled using Canadian data and are more easily interpreted and applied.

Next, studies that are broad enough such as the Aballéa study are generalizable, but will require certain localized inputs from the Canadian context within their modeling to be of use locally. Aballéa et al. created a model applicable to various European countries and broadly the interpretation of these results could be used for a local evaluation as well (Aballéa, et al., 2007). Studies based in the United States are likely to be relatively similar in population demographics and epidemiology, but are unlikely to be fully applicable because of differences in pricing of health goods and services as well as the typical clinical practice patterns for primary care and public health. With proper adjusting for prices, wages, and practice patterns, studies from the United States, such as the Clements study, are a useful supplement for local decision makers (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011). Studies based upon very specific situations or jurisdictions, such as the Buxton-Bridges study of employees at a Michigan automotive plant are more difficult to generalize (Buxton-Bridges, et al., 2000); however, it could

be applicable to other similar type employers interested in their respective workforces. For the purposes of a provincial policy maker though, studies which best match the jurisdiction and perspective are likely to be of greater value. The societal perspective is also more applicable to a broader policy making audience, though for some Canadian policy makers, the public health care system perspective may be of primary interest.

4.1.2 Results by Population Subgroup

Generally, the results of studies within each subgroup (pregnant and post-partum women, children and adolescents, healthy working age adults, and high risk individuals), were aligned in the same cost-effectiveness quadrants despite differences in perspective, design, intervention and comparator, inputs, and health care environment.

Firstly, vaccinating pregnant women was generally found to be cost-effective. Both studies that analyzed this population subgroup from the societal perspective found either a dominant result (Roberts, Hollier, Sheffield, Laibl, & Wendel Jr, 2006) or had an ICER of $7,718USD per QALY gained in 2004 United States dollars (Beigi, Wiringa, Bailey, Assi, & Lee, 2009)that was below the typical cost-effectiveness threshold in Canada, which has been stated to range from $20,000CAD to $100,000CAD per QALY (Cleemput, Neyt, Thiry, De Laet, & Leys, 2011). For post-partum women, vaccination was cost-saving (Ding, Zangwill, Hay, Allred, & Yeh, 2012). From the health care system perspective, all studies were considered cost-effective.

When looking at the evidence for children and adolescents, all included studies agreed that compared to no vaccination, vaccination is more effective in improving health outcomes, but depending on the age and risk of the children, cost-effectiveness varied. For younger children from the societal perspective, Esposito et al., Marchetti et al., Luce et al., and Cohen et al. found vaccination to be dominant (Esposito, et al., 2006; Marchetti, Kühnel, Colombo, Esposito, & Principi, 2007; Luce, et al., 2001; Cohen & Nettleman, 2000). As the age of children increased, so did the cost per QALY, reaching upwards of $79,000USD for children aged 5 to 11 years and over $100,000USD per QALY for young teens (Prosser, et al., 2006). This trend was most pronounced in low risk children. Overall, vaccinating older children was less cost-effective and was seen across all of the studies, regardless of risk. Younger children tended to derive more benefit from the influenza vaccine than older children and as a result, increased age was associated with an increased ICER. This likely stems from the incrementally greater improvement in health outcomes for younger children compared to older children. Younger

children have a higher risk of infection and are more vulnerable to the effects of infection, suffering a greater severity of symptoms and resulting in higher treatment costs and more hospitalizations. On the other hand, older children are less likely to suffer as severe health consequences and so the benefit realized from averting influenza infections is less impactful on the ICER. This age trend is best exemplified in the Prosser study, which examines the entire age spectrum of children (Prosser, et al., 2006). Infants and younger children in the Prosser study have a dominant or lower ICER than adolescents and teenagers.

Another finding in the literature for children and adolescents was the difference in TIV and LAIV as the intervention vaccine. LAIV was found to be more effective in children than TIV and so the use of LAIV in these studies often is cost-effective because of the greater improvement in health outcomes. This was found even despite a higher cost and best demonstrated in the Pitman study (Pitman, Nagy, & Sculpher, 2013).

Moving onto the next population subgroup of healthy working age adults and high risk adults, there was a mix of different results depending on specific population characteristics and model inputs. The cost-effectiveness of high risk adults was studied by looking at specific groups with a pre-existing risk of complications. In the Avritscher study, it was found that vaccinating working age cancer patients was extremely cost-effective from the societal perspective (Avritscher, et al., 2007). Similarly in the Blommaert study, vaccinating health care workers and adults with underlying illnesses was also clearly cost-effective from the perspective of the health care system (Blommaert, Bilcke, Vandendijck, Hanquet, Hens, & Beutels, 2014).

For lower risk healthy working age adults however, the results are less clear. To start, the Aballéa studies show that vaccinating healthy working age adults 50 to 64 years old in Europe was generally cost-effective (Aballéa, et al., 2007). These results provide more evidence to re-examine current seasonal influenza immunization policies which only provide publically funded vaccine to adults over 65 years old. The findings from the Aballéa studies question the validity of the current 65 year old “retirement cutoffs” and these age cutoffs should be potentially adjusted downward to include those about 50 years old. But a closer examination showed that even the results within the Aballéa studies vary between the countries examined. For instance, vaccinating all healthy working age adults 50 to 64 years old was found to be less costly, more effective, and dominant from the societal perspective in the Italian and German setting. But this was not the case in France and Spain where vaccination was more effective but also more

costly. Each country had different incremental uptake, medical costs, vaccine price, and productivity losses and hence the cost-effectiveness varied across the countries. What this speaks to is the sensitivity of the results for healthy working adults. This subgroup is large and diverse relative to the other subgroups and the health outcomes of infection are generally not as overtly severe. Additional studies such as the Lee study, Nichol study, Maciosek study, and Turner study also show that vaccination of healthy adults is generally cost-effective, but ICERs are relatively high (Lee, Matchar, Clements, Huber, Hamilton, & Peterson, 2002; Nichol, Mallon, & Mendelman, 2003; Maciosek, Solberg, Coffield, Edwards, & Goodman, 2006; Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006).

However, not all of the evidence suggests that vaccination is economically beneficial. The Buxton-Bridges study demonstrates that vaccination of working adults is not cost-effective. In this study, employees at a car manufacturing plant were vaccinated over two influenza seasons and the cost-effectiveness findings from both seasons were not in favor of vaccination. In the first season, it was found that vaccinated employees had more influenza like events, more days off work, all translating to an increased cost; but the difference was not statistically significant (Buxton-Bridges, et al., 2000). In the second season, vaccinated employees had fewer influenza like events, fewer days off work, but this still did not generate cost savings. These findings from the Buxton-Bridges study need to be understood with the context that the clinical efficacy trial (which was the basis for the economic evaluation) was conducted when the vaccine was mismatched to the circulating strain which significantly reduced vaccine efficacy. But even in the second season when there was a good match between vaccine and circulating strain, cost-effectiveness was not established. This study was from the third party payer perspective.

Similarly, the Mogasale study also found vaccination of healthy adults not to be cost-effective from the health care system perspective. Two studies clearly showed the polarity of the results: the Mogasale study and Newall study, both conducted in Australia and both evaluating healthy working adults 50 to 64 years old, but with opposing findings. The Newall study found that vaccinating this group compared to the standard policy (vaccination for adults over 65 years only) results in a slightly more costly but more effective strategy (Newall, Scuffhamd, Kelly, Harsley, & MacIntyre, 2008); the Mogasale study contested this finding and stated that vaccinating this group was expensive and not cost-effective from the health care system perspective (Mogasale & Barendregt, 2011).

The key differences driving the polarity of results between the Mogasale study and other studies are the assumptions on costing, resource inputs, and influenza incidence put into their respective models. Newall et al. used a great incidence rate of influenza infection than Mogasale et al.; other differences in model inputs also contributed to the contradictory results (Newall, Scuffhamd, Kelly, Harsley, & MacIntyre, 2008). For instance, Mogasale et al. ignored disability due to an influenza infection stating that an infection only occurs for a short duration of time and was negligible. Mogasale et al. also assumed a lower vaccination uptake for the current comparator policy and a higher uptake rate in the expanded intervention policy (Mogasale & Barendregt, 2011). The large difference in uptake rates caused a greater incremental cost difference between the two programs especially relative to other studies. Vaccine efficacy was also assumed to be lower in the Mogasale study than in the Newall study and other studies. The assumed efficacy of the vaccine at 16% reduction in ILI cases, 56% reduction in hospitalizations, and 33% reduction in deaths was lower in the Mogasale study compared to the Aballéa study which estimated a 29% reduction in ILI and a 68% reduction in deaths (Mogasale & Barendregt, 2011; Aballéa, et al., 2007). The Newall study used a 74% reduction in hospitalizations and deaths (Newall, Scuffhamd, Kelly, Harsley, & MacIntyre, 2008).

Overall, the results in healthy working age adults support vaccination, but in several studies the results were mixed and very sensitive to model inputs such as assumed vaccine efficacy, uptake, and lost productivity. Additional studies are likely necessary.

In terms of a broad population based intervention, both Clements et al. and Sander et al. identified that a universal program is cost-effective. In the Clements study, a dominant result was found for the U.S. population from society's perspective (Clements, Chancellor, Nichol, DeLong, & Thompson, 2011). What is perhaps more compelling and relevant to local policy makers is the Sander study, which uses a true before-and-after (pre-UIIP and post-UIIP in Ontario) set of inputs for the economic evaluation. Taken from the health care system perspective, Sander et al. found that the UIIP in Ontario was cost-effective (Sander, et al., 2010).

An essential factor in the study findings is the perspective taken in the analyses. The studies on pregnant and postpartum women were from the societal, third-party payer, and public health payer perspective. The societal perspective found that providing influenza vaccine to pregnant mothers was generally cost-effective. Ding et al. had a resulting net benefit, Roberts et al. found

a dominant strategy and Beigi et al. had a cost per QALY of approximately $10,000CAD(Ding, Zangwill, Hay, Allred, & Yeh, 2012; Roberts, Hollier, Sheffield, Laibl, & Wendel Jr, 2006; Beigi, Wiringa, Bailey, Assi, & Lee, 2009). However, from the third party payer perspective, these studies did not find good value for money in vaccinating pregnant women. The Ding study found that while the analysis from the societal perspective was cost-saving, the analysis from the third party perspective was at an increased cost (Ding, Zangwill, Hay, Allred, & Yeh, 2012).
A similar phenomenon occurred in the literature for children and adolescents, where only the societal and the health care payer perspective were used. Marchetti et al. and Navas et al. have dominant and cost-saving results for vaccinating children from the societal perspective (Marchetti, Kühnel, Colombo, Esposito, & Principi, 2007; Navas, et al., 2007). However, when the same analysis was from the health care system perspective, the results changed cost-effectiveness quadrants to increased effectiveness and increased cost. Similarly, this shift in results based on a perspective change is more pronounced with healthy working age adults. The Aballéa studies had a dominant result in Italy and Germany from the societal perspective but these results shifted cost-effectiveness quadrants when taken from the third party payer perspective (Aballéa, et al., 2007).

With a third party payer perspective, most of the studies did not find strong value for money in vaccinating healthy working age adults. This was similar to the findings with children and pregnant women, likely due to the fact that the third party payer perspective does not recognize and capture the broader benefits of immunization that a societal perspective would have.

That said, not all of the results across all studies changed cost-effectiveness quadrants by changing perspective. For healthy children aged six months to 13 years old, the results from the Salo study remained dominant in the societal and the health care system perspective (Salo, Kilpi, Sintonen, Linna, Peltola, & Heikkinen, 2006). Similarly, for healthy adults aged 50 to 64 years, the Turner study had only a slight change in ICER values when taking the health care system perspective compared to the societal perspective (Turner, Wailoo, Cooper, Sutton, Abrams, & Nicholson, 2006).

In summary, these changes in results demonstrate the importance of the perspective in an economic evaluation. The shift in perspective changes which costs are included in the analysis (and which are not included), leading to a difference in results. For the case of influenza

vaccination, a third party payer or a health care system perspective does not capture all the broad benefits and costs (such as productivity costs) that a societal perspective would capture.

Besides perspective, a change in the comparator within the same study also dramatically influences results. For instance, the Skedgel study actually has two analyses within the same economic evaluation (Skedgel, Langley, MacDonald, Scott, & McNeil, 2011). In one analysis, vaccinating all pregnant women was compared to not vaccinating pregnant women. In another analysis, vaccinating all pregnant women was compared to vaccinating high risk pregnant women. In the first scenario, vaccination was found to be more effective and cost saving (i.e. dominant); however, in the second scenario when the comparator was vaccinating high risk women, the incremental cost rose to $39,942CAD per QALY gained. A change in comparator had a large effect on the ICER calculation and significantly changed the results. Since the cost of vaccinating all pregnant women was relatively constant in both scenarios, the change was driven by the difference in health outcomes. Because the incremental gain in health outcomes in the first analysis was larger than in the second analysis, the ICER increased between the first and second scenario.

In the Cohen study a similar phenomenon occurred based on the difference between two interventions both being compared to a “no vaccination” comparator. In one analysis, a *flexible* setting (i.e. after-hours clinics) for children to be vaccinated was compared to no vaccinations at all. In the second analysis, a *restrictive* setting was compared to no vaccinations at all. Cohen et al. found that the flexible setting had a greater net benefit and cost-saving than the restrictive setting because of the impact of productivity costs (Cohen & Nettleman, 2000). The flexible setting allowed for parents and caregivers to bring their children to be vaccinated outside of work hours, significantly lowering the time taken off work and associated lost productivity, making the program more efficient from the societal point of view.

As shown with the Cohen study, in real life situations, the setting, logistics, human resources, processes, and administration have a significant impact on a program’s operating costs and opportunity costs. Some of the studies evaluated such programmatic considerations. The Luce study evaluated two programmatic scenarios: an individual-based program where caregivers were assumed to initiate a visit to a health care facility specifically for vaccination of the child, and a group-based program where vaccination was given in a group setting, such as a school or a child care facility, where caregivers were not involved, effectively eliminating all caregivers’

loss of time, productivity, and transportation costs associated with vaccination visits (Luce, et al., 2001). The results from this study, from the societal perspective, show that the group-based scenario was a dominant strategy while the individual-based program was a cost-effective strategy with greater incremental improvement in health outcomes as well as an incremental increase in costs.

In the same fashion, Schimier et al. also illustrated that a school-based vaccination program offered significant cost efficiencies compared to a primary care based vaccination program. This school-based program was delivered across 5 to 18 year olds and was found to be a cost-saving program with net savings of $171.96USD per household (Schmier, Li, King, Nichol, & Mahadevia, 2008). This method of school-based administration can simplify logistics, reduce travel time, and from a practical decision maker perspective, help appropriately forecast the amount of vaccine which needs to be purchased. With less time spent on the vaccination process itself, parents and caregivers do not lose work time and productivity. These kinds of programmatic differences can drastically affect the amount of time off work caregivers and parents need to spend to vaccinate their children; however, whether a school based program is an appropriate route for decision makers and whether parents are willing to accept this type of program can be contentious.

Even when considering the effects of lost productivity, the results for healthy working adults are mixed, depending on study design, cost assumptions, vaccine administration, and the country being studied. The Aballéa studies exemplify the subtleties of country-specific productivity losses. Across several countries, Aballéa et al. included country-specific inputs, accounting for productivity losses. The societal value of a workday lost varies considerably even among continental European countries. France and Germany (€216.64 and €226.26) have higher productivity losses than Spain and Italy (€130.66 and €164.91) and the number of days taken off for infection is higher in Italy (Aballéa, et al., 2007).

Since for working age adults a major component of cost-effectiveness decisions is based on lost productivity, it is important to recognize that productivity losses vary significantly by jurisdiction, and that results from any economic evaluation need to be adapted for localized decision making. Local wages have a major impact on the valuation of productivity lost. In terms of fairly determining the cost-effectiveness of a program, the link between wages, lost productivity, and cost-effectiveness may not seem entirely equitable. If it is true that a person's wage is the main

measure of lost productivity to society, then this may imply that only those with high wages are more valuable to society than those with lower wages. By virtue of this reasoning, it could also be implied that it is more cost-effective to protect workers with high wages and less cost-effective to provide vaccinations to lower wage workers. This point is further discussed in the next section.

Besides wages and lost productivity for working adults, another major factor affecting cost-effectiveness is the age-associated risk of infection and illness severity of the subgroup. Although this is true across the entire spectrum of the population, only the studies on children and adolescents stratified ages into smaller subgroups. As mentioned previously, in the Prosser study the degree of cost-effectiveness changed as the age and associated risk of children changed, and so it would be of interest to investigate smaller age subgroups within the broad age range for healthy working age adults (Prosser, et al., 2006). The age range of healthy working age adults is wide, from 18 to 64 years of age. A younger employee who just entered the workforce is very different than a seasoned employee who is heading into retirement. Therefore breaking the large age range down to smaller subgroups similar to those seen in the studies for children and adolescents would logical. This point is also discussed in the next section with specific examples from other reviews.

4.2 Comparison to Other Reviews

In addition to the included studies for this review, other literature can also provide insight and external validation of the results.

4.2.1 Healthy Children and Adolescents

Three other systematic reviews were conducted in 2008, 2011, and 2012 by Savidan et al., Nichol et al., and Newall et al. respectively, examining the economic evaluation evidence for seasonal influenza immunization programs for healthy children (Savidan, Chevat, & Marsh, 2008); Nichol, 2011; Newall, Scuffham, Kelly, Harsley, & MacIntyre, 2012). Aligned with the findings of this thesis, Savidan et al., Nichol, and Newall et al., conclude that vaccinating children is likely to be cost effective, although certain parameters can influence the degree of cost-effectiveness or cost-savings.

There is overlap in the included studies among all of these reviews. Five of 15 studies from the Savidan review, 10 of 20 studies from the Nichol review, and 12 of 20 studies from the Newall

review were the same studies included in this review. This would have an effect in the alignment in results. Some of the studies included in these other reviews were not included in this thesis due to manual title screening which may have missed these studies. For example, the Riddough study from 1983 and the Weycker study from 2005 had titles, “Influenza Vaccination” and “Population-wide benefits of routine vaccination of children against influenza” respectively, which could have been include into the thesis (Riddough, Sisk, & Bell, 1983; Weycker, et al., 2005). Other studies were intentionally removed because of lack of relevance to the research objective or removed because of quality. Studies such as the Dayan study, based in Argentina, was excluded due to geographic relevance (Dayan, Nguyen, Debbag, Gomez, & Wood, 2001). The Meltzer study was included in the Savidan review, but was removed from this thesis due to low quality (Meltzer, Neuzil, Griffin, & Fukuda, 2005).

Although in the Savidan review, no systematic quality appraisal was performed, the results of the included economic evaluations were similar to the results found in this current review. Savidan et al. found that for healthy children, most of the published evidence indicates that vaccinating children is cost-effective or cost-saving (Savidan, Chevat, & Marsh, 2008). Similar to the trend seen in this thesis, this result was more pronounced for children who were at high risk and younger. Of the 15 studies in the Savidan review, ten concluded that vaccinating children was cost-effective or cost-saving, three studies found that only under certain conditions would vaccinating children be cost-effective or cost-saving, and the remaining two studies found that vaccinating children was neither cost-effective nor cost-saving under any condition. The conditions or parameters evaluated in the studies were age, degree of risk, and administration method (group or individual). In the studies that did not find a cost saving or cost-effective result for vaccinating young children, indirect benefits such as a reduction of transmission of influenza to adults were omitted and these studies were also taken from the third party payer perspective. An overall conclusion made by Savidan et al. was that the literature examining children was diverse and that the design and inputs of the economic evaluations varied significantly, causing difficulty in summarizing findings(Savidan, Chevat, & Marsh, 2008). Newall et al. had a similar conclusion. The Newall review generally found vaccination to be cost-effectiveness in children, but with several important caveats (Newall, Scuffham, Kelly, Harsley, & MacIntyre, 2012). First, the literature regarding children did not have a standardized method of measuring efficacy or effectiveness of the vaccine. Often ILIs are used, but even the definition of ILI varied across studies. Using non-specific endpoints influences the efficacy inputs used in economic models. The Nichol review included similar studies from the Savidan review and Newall review and so

concluded that vaccination of children is generally cost-effective even with the omission of the effect of indirect protection (Nichol, 2011). The authors also indicate that immunizing children confers an indirect protection to the rest of the population; however, the included studies often do not account for this and likely resulted in an underestimation of the cost-effectiveness of vaccination (Savidan, Chevat, & Marsh, 2008; Nichol, 2011; Newall, Scuffham, Kelly, Harsley, & MacIntyre, 2012). In this thesis as well as all of the previous reviews, this was highlighted as a clear future research need. Only a select number of studies crudely accounted for indirect protection. Also mentioned in the Newall review were differences in social contact in different populations and its potential effect on transmission (Newall, Scuffham, Kelly, Harsley, & MacIntyre, 2012). Social contact differs from setting to setting and across ages; for instance, younger children in daycare should be modeled differently than older children in high school since their level of social contact among each other and with others outside of the age group varies.

4.2.2 Healthy Adults and Workers

With regard to healthy adults, three reviews studied working age adults (Gatwood, Meltzer, Messonnier, Ortega-Sanchez, Balkrishnan, & Prosser, 2012; Wood, Nguyen, & Schmidt, 2000; Postma, et al., 2002). The Wood review, conducted and published in 2000, included six economic evaluations with perspectives from the employer and society. The Postma review, conducted two years later, included 11 economic evaluations; the Gatwood review had seven studies. Overlap with these reviews was relatively low, with one of six studies from the Wood review, three of seven studies from the Wood review, and two of 11 studies from the Postma review being the same studies included in this review. Studies were intentionally removed because of lack of relevance to the research objective, or removed because of quality. For example, the Burkel study which was based in Brazil, was excluded due to relevance(Burckel, et al., 1999). The Kumpulainen study was included in the Wood and Postma reviews, but was removed from this thesis due to low quality (Kumpulainen & Makela, 1997).

As with this thesis, these reviews found considerable variation in the results for healthy adult workers. All authors found that generally, cost-effectiveness was not strongly demonstrated in the literature and only under certain circumstances was it clearly favorable to vaccinate healthy working age adults. Perhaps more than the studies for children and adolescents, cost-effective results in working age adults varied widely by the conditions, inputs, and assumptions. As with other population subgroups, the reasons for the variation in results were driven by a few key

study parameters. Results were sensitive to changes in the case definition of influenza (ILI, LCI, other definitions), the incidence or attack rate of the circulating strain, estimates of vaccine effectiveness, and the calculation of costs such as the indirect costs of the illness (time off work, productivity, symptom relief).

Firstly, the specific definition of influenza infection varied widely in the literature for healthy working adults. Wood et al. mentioned that different definitions of cases of infection across studies made summarizing results difficult (Wood, Nguyen, & Schmidt, 2000). While certain studies used broader definitions of "influenza" there were no consistent, standardized, and specific indicators of diagnosis. Even within the term "influenza-like illness," variation existed. By association, vaccine efficacy was also variable due to differing definitions of influenza or of ILI.

Next, the incidence of influenza in adults significantly influenced results and varied widely across studies. This point was brought up in the Gatwood review, where the included studies had a range of incidence of ILI from 5% to 15% (Gatwood, Meltzer, Messonnier, Ortega-Sanchez, Balkrishnan, & Prosser, 2012). As influenza infectivity changes annually, incidence is a particularly complicated parameter to estimate and is especially hard to measure for adults. Many adults may not even recognize their symptoms as an influenza infection or may ignore the infection completely.

Internationally, workers are paid at different rates and this is clearly a reason for differences in valuations of lost productivity. However, even within the same country wages differ from industry to industry and using a national average salary as an input in an economic evaluation to value the time or absentee days lost to influenza, can be a crude, unspecific, and not entirely accurate method. In fact, average wage rates may not accurately reflect the true value of time. Yet, when specific wages within a country, industry, and even a specific company are examined, an interesting result emerges. Within the Wood review and the Postma review, there was an interesting mention of working employees and special points regarding the specific nature of evaluating the cost-effectiveness for workers. The Wood and Postma reviews noted that the *type* of worker infected had a significant impact on the cost-effectiveness results (Wood, Nguyen, & Schmidt, 2000; Postma, et al., 2002). Similar to findings found in this thesis, labour costs across studies varied as it would across countries—but also across industries, and even across functions within a company. As mentioned in the previous section, an individual's wage has a considerable effect on cost-effectiveness results. Time lost due to the influenza infection

such as absentee time is often valued at the rate of that individual's wage per duration of time. Both Wood et al. and Postma et al. included the Burkel study which evaluated the cost-effectiveness of influenza vaccination within a Brazilian pharma-chemical company (Burckel, et al., 1999; Wood, Nguyen, & Schmidt, 2000; Postma, et al., 2002). In this company, there were several different corporate hierarchical levels from operations, support, management, and executive management. Each of these levels was paid a specific salary in accordance to their role and degree of responsibility within the company, with the cost of a lost day's productivity ranging from $156USD to $2,066USD. This salary range led to differences in the value of a lost day and consequently, to differences in the cost-effectiveness of the influenza vaccination based on the employee's level within the same company. Differences in salaries and associated cost-effectiveness imply that individuals with a higher salary have greater potential productivity losses and therefore, are technically more cost-effective to vaccinate than those with lower salaries.

Workers differ in location, salary, and age, but additionally, the *nature* of their occupation and type of work may affect their level of social contact and interaction with higher risk groups. An individual working from home as a web designer has a different level of exposure to influenza than a retail salesperson which would also be different from a nurse working in a hospital ward.

In addition to the variability of job type and salary, the definition of "healthy working adult" is not specific in the age range it encompasses. Healthy working age adults are usually considered to be within 18 to 64 years of age. However, there are clear physiological, societal, and behavioral differences within this broad age group. When it comes to influenza infection, an 18 year old worker may have a different set of symptoms, outcomes, resource use, and duration of infection than a 64 year old worker. It is more likely that an older adult would suffer a longer, more severe infection. At the same time, it is also more likely that an older adult has a greater salary than a younger employee and therefore a work day lost due to influenza infection is more costly to an employer and to society.

Given all of these factors in determining cost-effectiveness for this subgroup, it would be useful when studying healthy working age adults to adopt narrower age range stratifications; one such stratification that would provide more detail would be to use the age categories that Statistics Canada uses in their analyses of the population. These five-year age groups are used for adults greater than 25 years old (25 to 29, 30 to 34, 34 to 40, etc.) and this breakdown could be used

as a standard in future economic evaluation (Statistics Canada, 2015) to allow a more thorough examination of each age group in more detail. Further stratification could possibly be conducted by industry, by wages, and also by the nature of the occupation for healthy working age adults.

Ultimately, the working-age population is a diverse mosaic which current evidence does not address particularly well. These reviews indicate that there are several key parameters which can influence results. It is clear that the incidence of influenza, the definitions of influenza, vaccine uptake, efficacy, and costs of the immunization program, and the indirect benefits of vaccination are the main parameters to an economic evaluation and need to be carefully defined to make definitive or distinct conclusions. Indirect benefits such as the reduction in transmission through herd immunity, the associated productivity gains, and derived future immunity from one season to the next, are also critical to developing an immunization policy for healthy working adults.

4.2.3 Pandemic Influenza

To further complement the evidence on seasonal influenza, a systematic review was conducted in 2012 by Velasco et al. that investigated the economic evidence regarding preparedness strategies and interventions against influenza *pandemics*(Valesco, et al., 2012). Different in its scope to this thesis, the Velasco review included economic evaluations of health interventions against pandemic influenza such as non-pharmaceutical strategies (social distancing, closure of public spaces and community services), pharmaceutical treatment strategies (anti-viral medications), and preventative strategies (anti-viral prophylaxis and mass vaccination). Velasco et al. included economic evaluations from United States, Canada, United Kingdom, Australia, Netherlands, France, and Singapore. Interventions were stratified into “general population,” which provided the intervention for all the public, and “targeted population,” which provided the intervention for high risk populations only.

Interestingly, Valesco et al. found that providing health interventions to the general population or only to a targeted group did not have a significant impact on incremental costs(Valesco, et al., 2012). With respect to vaccination specifically, Valesco et al. found that the most cost-effective interventions compared to no intervention were vaccination alone, vaccination combined with anti-viral prophylaxis, and vaccination coordinated with school closures. Vaccination for the general population generally had ICERs which demonstrated good value for money (<$25,000 per QALY). Vaccination interventions aimed at targeted populations only were found to have

higher ICERs (>$100,000 per QALY), compared to no intervention. As with any comparison across studies, each economic evaluation had its own setting, perspective, and range of perspectives, so the most cost-effective intervention against pandemic influenza remains unclear. Attempting to select only the high risk individuals for a prevention program during a pandemic is difficult in practice and likely not cost-effective. This practical limitation may be applicable to seasonal influenza as well.

While the Valesco review was studying pandemic influenza and excluded seasonal influenza studies, the results are relevant to this thesis. Pandemic influenza has a more acute impact on the population and different interventions that could logically be used could not be used for seasonal influenza. Closures of public spaces and community services are unlikely to be feasible for seasonal influenza. However, preventative programs via vaccination are common to both pandemic and seasonal influenza. Integrating the evidence available from the Velasco review as well as this thesis demonstrates a trend towards providing vaccine to the general public (i.e. universally providing publically funded influenza vaccine) as a cost-effective intervention when managing either pandemic or seasonal influenza.

4.2.4 Variations across Geographies

International specificity of inputs was discussed in a recent review by Peasah et al. in 2013 on the cost-effectiveness of global influenza immunization programs (Peasah, Azziz-Baumgartner, Breese, Meltzer, & Widdowson, 2013).This review examined the economic evidence regarding influenza immunizations across several countries and distinguished between high income and middle-high income countries, defined by GDP levels. The Peasah review identified significant differences in the inputs used in immunization programs evaluations, even among countries in the same income level. For instance, Peasah et al. found that hospitalization costs in North America were significantly higher than Europe and Asia (excluding Japan) (Peasah, Azziz-Baumgartner, Breese, Meltzer, & Widdowson, 2013). Variations of study methodology, costing, health systems, and other assumptions contributed to large differences in the results.

Even cultural differences were significant; absenteeism was found to be lower in Asian countries such as Hong Kong, reducing the calculated lost productivity compared to Western countries. Peasah et al. found that for subgroups such as children, pregnant women, and elderly citizens, influenza immunization was found to be cost saving or at least cost-effective in various locations (Peasah, Azziz-Baumgartner, Breese, Meltzer, & Widdowson, 2013). Results for adults were

mixed as seen previously. There were significant gaps in evidence regarding pregnant women and health care workers in the Peasah review and a future research suggestion mentioned by the authors was to standardize methodological approaches and utilize common parameter definitions. This conclusion further reinforces the fact that model variations need to be made consistent across geographies to allow for better cross-study comparisons and more appropriate evidence-based recommendations for decision makers.

4.3 Provincial Policies and Implications

As of June 2015, immunization policies differ across Canada, with six provinces (Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, Newfoundland) and all three territories (Nunavut, Yukon Territory, Northwest Territories) offering universal influenza immunization programs. Three provinces (British Columbia, Quebec, New Brunswick) provide targeted influenza immunization programs. From even within the groups of provinces offering targeted programs, there were differences with some provinces including certain high risk groups while others did not. A similar but subtle policy difference exists for provinces with universal programs as well, with public health promotions being focused on high risk groups in Yukon, Saskatchewan, Manitoba, and Nova Scotia. In Ontario, Alberta, Nunavut, and Northwest Territories, the universal immunization program is promoted to all residents across all ages and groups. Clearly the national influenza immunization picture is a mosaic of several different pieces, each developed independently of one another and from province to province. This method of protecting the public from influenza infection may benefit from a re-evaluation of the currently available evidence and perhaps be more effective and more equitable for all Canadians as a single national *policy*—and evolving to become a national immunization *strategy*.

The idea of a unified national immunization program, inclusive of influenza, was recommended by the Canadian Public Health Association in 2001 in a report submitted to the Commission on the Future of Health Care in Canada (Canadian Public Health Association, 2001). In this report, the recommendation of “a national review and decision-making process on vaccines that aims for consistency across provinces” was suggested. A unified approach could provide the foundations for a national immunization program, with set national guidelines and standards, of which the provinces would be tasked with implementation (Canadian Public Health Association, 2001).

However, a “one size fits all” policy where all Canadian provinces and territories adopt the same immunization program may not seem to be a realistic option at the present with differences in provincial governments, health systems, and budget priorities. Coverage rates among provinces also differ and could affect cost-effectiveness calculations by province. Additionally, the risk of vaccine wastage could increase with the introduction of a larger universal program. Ultimately, the specifics and best practices of a universal program might be best learned from the Ontario UIIP experience.

When it comes to programmatic differences, targeting risk groups, whether elderly adults or young children, for an immunization program can create difficulties for front line health care professionals who are expected to understand, communicate, and enforce policies which introduce inequity for residents. One simple example may be a nurse denying vaccination to a child who has grown outside of the age range considered to be “high risk.” This nurse would have to explain to the child’s parents or caregiver that the vaccination received last year was without cost, but that this year would now carry an out of pocket cost. The same would apply for a physician explaining to a 64 year old adult that he or she is under the age range of 65 years old and therefore needs to pay for vaccination. It is difficult to impose age cutoffs of 60 months for children or 65 years for adults. Education and enforcement with regard to these age cutoffs take time from front line health care professionals and may be misconstrued by the public as arbitrary, unaccountable, and potentially unfair. Screening and enforcement of criteria can be complicated and are often managed by front line health care professionals who may not have the training or desire to strictly enforce said policies. The issue extends to broader policy as well; not only are age and household criteria difficult to manage but criteria based on political borders can be also even harder to explain and justify.

There may be concern that since vaccination rates are generally low that the introduction of a universal program may result in wasted spending; however, data from a study in Ontario show otherwise. Using data from the 1996-97 National Population Health Survey and the 2000-01, 2003, and 2005 Canadian Community Health Survey, Kwong et al. describes in a report to the Public Health Agency of Canada, the increase of vaccination rates upon the introduction of UIIP in Ontario(Kwong, et al., 2008). Compared to other provinces at the time, after implementing UIIP, Ontario had a consistently higher vaccination rate increase for the population aged >12 years old than other provinces after implementing UIIP, rising 28 percentage points from 18% to 42% of the population. Comparatively, other provinces averaged an increase of 15 percentage

points from 13% to 28% of the population. Uptake rates were stratified into three age groups, 12 to 49 years old, 50 to 64 years old, and >65 years old. As of a survey taken in 2005, the lowest uptake rates were in the 12 to 49 years group at 30% in Ontario and 16% in other provinces, and rising in the 50 to 64 years group at 50% in Ontario and 30% in other provinces, and highest in the >65 years group, at 74% in Ontario and 62% in other provinces. A universal vaccination program could potentially be adopted as an additional mechanism to improve uptake across the population.

While these results are encouraging, seasonal influenza is still often overlooked as a major threat to health, even as it is contributing to illnesses, hospitalizations, and deaths of many Canadians each year. Despite these facts regarding influenza, vaccine uptake is still relatively low in Canada. The included studies in this thesis generally used assumptions or performed sensitivity analyses and tested different scenarios that were in line with the uptake rates in Canada. For pregnant and post-partum women, most of the studies did not explicitly state an assumed uptake rate. However, the Ding study, Jit study, and Blommaert study clearly mentioned an assumed uptake rate of approximately 45% in the Ding study and Jit study, and 50% in the Blommaert study (Ding, Zangwill, Hay, Allred, & Yeh, 2012; Jit, Cromer, Baguelin, Stowe, Andrews, & Miller, 2010; Blommaert, Bilcke, Vandendijck, Hanquet, Hens, & Beutels, 2014). For children and adolescents, base case assumed uptake rates ranged widely in the literature from of 10% which was a low uptake scenario in the Pitman study, to upwards of 97% in the Esposito study (Pitman, Nagy, & Sculpher, 2013; Esposito, et al., 2006). Generally, the studies used rates between 30% to 50% for children and adolescents. For healthy working age adults, the uptake rates for the Aballéa study are most robust and accounted for the effects of a “universal” program. In the evaluation, Aballéa et al. used uptake rates from the existing policy, but also used a “new” uptake rate if the policy was expanded to all adults 50 to 64 years old (Aballéa, et al., 2007). For example, in Germany, Aballéa et al. assumed that with an expanded policy for all adults, vaccination rates would increase from 39% to 53% in high risk adults and 16% to 41% in low risk adults, mimicking the effect actually seen in Ontario with the introduction of UIIP in that a more expanded open immunization program has the additional benefit of increasing uptake rates.

Another potential option to increase vaccine uptake rates is simply to mandate it. Mandating vaccination has arisen as a policy option to increase vaccine uptake—an option that may or may not be the right one for Canadians. Of particular interest is whether there is a need for a

policy of mandatory vaccination for front line health care workers. Health care workers currently are recommended to receive publically funded influenza vaccination in Canada (Public Health Agency of Canada: National Advisory Committee on Immunization, 2014); however, the question of a policy of voluntary versus mandatory vaccination remains. Although slightly dated, the 1991 Yassi study which was in the Postma review, found that vaccinating health care workers was cost-effective from the perspective of the hospital and society, even with a low vaccine uptake of approximately 10% (Yassi, Kettner, Hammond, Cheang, & McGill, 1991; Postma, et al., 2002). Additionally, the newer 2014 Blommaert study concluded that, assuming no indirect protection, there is evidence of cost effectiveness in vaccinating health care workers with an incremental cost of €24,096 per QALY gained (Blommaert, Bilcke, Vandendijck, Hanquet, Hens, & Beutels, 2014). With indirect protection, this ICER shifts to a cost-saving result.

In British Columbia, health authorities implemented a policy which expected health care providers in hospitals to be vaccinated or at a minimum wear a mask to protect hospital patients. This was met with resistance and the British Columbia Nurses Union unsuccessfully launched a grievance with the British Columbia Labour Relations Board (Ksienski, 2014). The Canadian Federation of Nurses Unions does not support any program or policy that requires mandatory influenza immunization for nurses or any other health care worker (Canadian Federation of Nurses Unions, 2012), yet the Canadian Nurses Association issued a position statement considering mandatory immunization policies by employers to be congruent with the Code of Ethics for Registered Nurses in Canada and the obligation to act in the public interest (Canadian Nurses Association, 2012). Front line health care professionals are considered as a high risk population by NACI (Public Health Agency of Canada, Canadian Nurses Coalition on Immunization, Canadian Pharmacists Association, 2015)and hospitals and primary care clinics are places where significant contact and exposure with the influenza virus exists, yet there is conflicting direction regarding mandatory policies for vaccination (Ikura, Doig, & Laupacis, 2014). Whether a true mandatory influenza vaccination policy should be or can be implemented successfully as hospital policy will need to be determined in the future, balancing ethical considerations, the political nature of hospital administration, and most importantly, patient needs.

From the population subgroups which emerged from the literature, it was found that the evidence from the societal perspective, for children and adolescents, pregnant and postpartum

women, high risk groups, and to a limited degree, healthy working age adults, providing vaccination is generally cost-effective. The evidence is supportive of vaccination but mixed and weaker in healthy working adults. These are conflicting results which merit further investigation especially at a local provincial level.

In addition to the summary of the current cost-effectiveness evidence regarding influenza immunization programs, this thesis also compares and contrasts current provincial programs in Canada. Given the considerations to run an influenza immunization program, it would be warranted to re-evaluate the feasibility of adopting a unified, consistent immunization policy against influenza. Particularly in provinces such as British Columbia, New Brunswick, and Quebec where targeted immunization programs still exist, re-evaluating the criteria of "high risk" and whether a universal immunization program would be acceptable or beneficial to adopt is warranted. The Sander study in particular is effective in identifying some key parameters that other provinces would need to investigate in adopting a similar UIIP as the one in Ontario (Sander, et al., 2010). Looking to other jurisdictions internationally would also be important to learn and adopt best practices. Although lesser in population that Canada, national universal influenza immunization programs do exist in other countries such as Austria and Finland and could be further examined to understand best practices in implementation (Mereckiene, et al., 2010).

The landscape for influenza immunization in Canada is still a patchwork of provincial programs, and in the future, a national program may be more beneficial in terms of health outcomes and costs as well as logistics and administration. This would improve protection against infection, streamline administration and operations, and provide fairer and more equitable access for all Canadians.

4.4 Implications and Transferability of Findings

This thesis addresses the programmatic discrepancies in Canada and reflects on the cost-effectiveness evidence of influenza immunization programs. Several stakeholders may have a significant interest in the findings of this research. Implications exist for decision makers and researchers in health policy, health economics, epidemiology, and for families and individuals as well.

4.4.1 Public Health Agencies

Public health officials need updated evidence to make the best decisions in developing and investing in programs to improve the health of the community. The implications of this thesis are important to several levels of public health, from federal to provincial public health agencies and officials. This thesis provides a summary of cost-effectiveness evidence which generally support NACI's recommendation of influenza vaccination for all individuals aged 6 months and older, similar to provinces with UIIPs like Ontario. The thesis also describes provincial discrepancies in public vaccination programs and provides evidence to investigate whether provincial coordination across Canada is a viable option to consider.

4.4.2 Health Economists and Epidemiologists

Health economists and epidemiologists may use these findings in their own research into influenza immunization programs. As influencers of decision and policy makers, health economists and epidemiologists require relevant information for producing technical reports, models, and health technology assessments. Findings from this thesis can be used to model immunization programmatic scenarios, understand policies, and provide recommendations on the cost-effectiveness of adopting different programs. The use of the quality appraisal results can help guide modelers in deciding which assumptions can be taken to construct sensitivity analyses relevant to their local setting. For instance, the lack of the incorporation of herd immunity in many of the analyses reveals that health economic modelers should consider this when providing localized models for decision makers. Other design considerations which are important would be the specific definitions of vaccine efficacy. Many of the studies will require a refinement in how efficacy was measured. For health policy researchers, the qualitative results that describe the discrepancies in vaccination programs across provinces would be useful.

4.4.3 Health Care Professionals

For front line health care professionals that manage and administer influenza vaccines, the findings from this thesis are important to their practices. For physicians, nurses, and pharmacists who are permitted to administer vaccines, a universal compared to a targeted influenza immunization program will change how they can best take care of patients. A universal immunization program would offer the broadest coverage for all patients and may be beneficial for health care professionals as a simpler and more efficient way of providing influenza vaccine. Understanding both the clinical effectiveness and the cost-effectiveness of various programs will

also be important in the education of health care professionals as advocates for appropriate influenza vaccination and to ensure that vaccine uptake improves.

4.4.4 Individuals, School Boards, and Families

As the end users of immunization programs, individuals in the community are ultimately the most affected by the findings of this research. Realizing that such discrepancies exist in Canada, residents in provinces without UIIPs may wish to raise this issue with their local policy makers and politicians to advocate for changes in their province's policy. Particularly with school-aged children, school boards would also find the results for children and adolescents important for their part in preventing students from becoming ill and missing from classes. Understanding that influenza immunization is an important method for protecting themselves, their families, and other citizens in the community they live in, the public may be more inclined to receive influenza vaccination.

4.5 Limitations of this Research

Within this thesis, limitations exist. It is possible that studies may not have been captured in the search strategy and included in this research. While best efforts were taken to include as many relevant studies, other databases may have other studies that could have contributed to the analysis. Additionally, during title and abstract screening, some studies may have been missed. Quality appraisal in this review could also have been performed using more specific tools. For instance, several included economic evaluations were performed using models. Instead of only using the SIGN and the adapted WHO economic evaluation checklists, a checklist specific to appraising models such as the "Phillips Checklist," a quality appraisal tool specific to modeling, could have also provided an additional appraisal of quality (Philips, et al., 2004). Additional reviewers during the screening of titles and abstracts as well as during the quality appraisal stage would also have been beneficial to strengthen this systematic review.

A meta-analysis to synthesize cost-effectiveness point estimates from economic evaluations was not performed. Instead, a qualitative approach was taken to summarize and report results. While a meta-analysis is a valuable technique to consolidate results, the nature of economic evaluations is that they are designed with a highly specific objective and jurisdictional issue to address. This means that each economic evaluation has localized assumptions, design, costing, and inputs all of which make each evaluation unique and difficult to compare across or pool with other evaluations. In summary, while the lack of a formal meta-analysis is a weakness of this

review, using a qualitative approach was a conservative approach to avoid potentially misleading results.

For the policy research section of this thesis, it may be informative to include interviews with policy makers from each provincial public health agency in the future. This could offer additional insight and rationale for the decisions made on current immunization program structures as well as policies from the past.

4.6 Future Research

This work provides new insights into the cost-effectiveness evidence currently available across several population subgroups, including children and adolescents, pregnant and postpartum women, high risk adults, and healthy working adults. In addition to a systematic literature search, a comparative analysis of Canadian policy revealed programmatic discrepancies across provinces and territories.

Further research could be performed by a careful meta-analysis or pooling of the results from the included economic evaluations. While this has some methodological challenges, a meta-analysis with thorough caveats and statistical adjustments for heterogeneity in the inputs, study design, and settings could potentially provide interesting hypothesis generating findings.

Research could be performed on specific populations outside of those in this thesis. For example, a deeper exploration could be performed on certain groups and jurisdictions in Canada such as First Nations and Inuit populations, who are identified as high risk to complications due to influenza.

There is continued debate among the public regarding the risks and benefits of vaccination, including influenza vaccines. As a result of these debates, there is fear and confusion for parents and families about receiving vaccinations. This effectively could reduce vaccination uptake in the community and lessen the effects of herd immunity as well. Future research should be conducted to ascertain the educational needs as well as the reasons for refusing influenza vaccinations.

Additional research could examine future influenza vaccines. As there are several new emerging vaccine technologies, it would be a fruitful research endeavor to examine meaningful

differences in new types of vaccines, across specific risk groups, and the entire population as a whole. For instance, adjuvants to ameliorate vaccines, new delivery devices, or vaccines based on non-egg manufacturing could be examined from a cost-effectiveness perspective. Literature included in this review also only studied trivalent vaccines which contain three strains of the influenza virus. Future reviews could include economic evaluations of newer quadrivalent vaccines which contain four strains of the influenza virus.

As a foundation for future research, new hypotheses could be developed regarding the cost-effectiveness of policies and if alternative programmatic structures and systems could be more cost-effective than current ones. For instance, could primary care vaccination programs be shifted from physicians' exam rooms to community venues and mass vaccination clinics? Or could children be more cost-effectively protected with school-based programs? Should sports venues be a place for mass vaccination clinics? What other programmatic considerations could be implemented to increase vaccine uptake? There are several new exciting research questions that can stem from the insights of this research.

5 CONCLUSIONS

From the societal perspective and in many cases the health care system perspective as well, seasonal influenza vaccination was generally found to be a cost-effective strategy.

Vaccinating all pregnant and postpartum women against seasonal influenza compared to only vaccinating high risk pregnant and postpartum women was generally cost-effective. If indirect protection from mother to neonate was considered in the analysis, vaccination was especially cost-effective or in some cases, a dominant strategy.

Similarly, vaccinating all children and adolescents against seasonal influenza was generally cost effective, with robust evidence for infants, toddlers, and adolescents. If indirect protection from children to parents, caregivers, and household was considered in the analysis, vaccination was especially cost-effective or in many cases, a dominant strategy. School-based mass vaccination programs which reduced time off work for parents and caregivers to take their children to be vaccinated were found to be beneficial in reducing lost productivity and contributed to cost-effectiveness of the program.

The cost-effective evidence for vaccinating healthy working age adults (18 to 64 years old) was mixed and sensitive to inputs based on geographic location, vaccine efficacy, and valuation of

lost productivity. This result reflects the diverse nature of this large age subgroup. Indirect protection was generally not considered in the studies for healthy working age adults and could have impacted results. Vaccinating high risk adults with other co-morbidities, such as cancer and diabetes, against seasonal influenza was found to be cost-effective. Vaccinating health care workers against seasonal influenza was found to be cost-effective even without considering indirect protection; if indirect protection was incorporated into the model, the results were cost saving and dominant. Vaccinating elderly adults (>65 years old) was cost-effective.

Overall, universal mass immunization programs were favoured as a cost-effective strategy. Programmatic considerations such as administration, and incremental uptake rates were important to the sensitivity of the results.

As of June 2015, influenza immunization policies differ across Canada, with six provinces (AB, SK, MB, ON, NS, NL) and all three territories offering universal influenza immunization programs and three provinces (BC, QC, NB) providing targeted influenza immunization programs. Differences also exist with regard to the groups offered vaccine in provinces with targeted programs and with regard to how the vaccine is promoted in provinces that offer a universal program.

Additional research and reviews into new influenza vaccine formulations such as quadrivalent vaccines and the inclusion of new technologies and programmatic strategies would provide more insight regarding immunization policy decisions.

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