ECONOMIC EVALUATION OF AN INFLUENZA IMMUNIZATION PROGRAM

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ABSTRACT

Objective: To estimate the cost-effectiveness of an influenza immunization strategy directed at healthy children 36 months to 15 years on the herd immunity of entire communities, versus not implementing this strategy.

Design: An economic evaluation, cost-effectiveness analysis (CEA). Costs and effects were estimated jointly with a two-stage bootstrap with shrinkage correction. Uncertainties around input parameters were tested with one-way and multi-way sensitivity analysis.

Data Sources: Effect and resource consumption data were from the Hutterite Influenza Prevention Study. Unit costs were collected from multiple sources including, government reports and schedules, local suppliers, peer-reviewed articles and systematic reviews, Internet searches and study data on file.

Main Outcomes: Mean costs and effects, incremental cost-effectiveness ratio (ICER), net monetary benefit (NMB) statistic and cost effectiveness acceptability curves (CEAC).

Main Results: The average cost per patient in the treatment arm was estimated to be $69.08 and $32.66 in the control arm. The average number of influenza-free cases was of 0.96 in the treatment arm and 0.73 in the control arm. ICER was $164.19 per case of influenza averted, 95% confidence interval $28.38, $2,767.75. CEAC created from NMB showed that at a willingness to pay of $177, the probability of the treatment strategy being cost effective compared to the control was 0.50. Results from sensitivity analyses were slightly different

compared to base case results, supporting the robustness of base case estimates.

Conclusion: This strategy is likely to be cost effective relative to the comparator as the ICER estimate is low and because the estimate is conservative given that the study population was very healthy and the influenza season was mild. A more virulent season and a less healthy population would have produced a lower ICER or seen the treatment arm dominate the control.

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LISTS OF ABBREVIATIONS AND SYMBOLS

ABBREVIATIONS

CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CEP	Cost Effectiveness Plane
CI	Confidence Interval
CRT	Cluster Randomized Control Trial
CUA	Cost Utility Analysis
ER	Emergency Room
GEE	Generalized Estimating Equation
ICER	Incremental Cost Effectiveness Ratio
MLM	Multilevel Modelling
NMB	Net Monetary Benefit
NOTL	Niagara on the Lake
OCCI	Ontario Case Costing Initiative
OHIP	Ontario Health Insurance Plan
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency of Canada
QALY	Quality Adjusted Life Year

LISTS OF ABBREVIATIONS AND SYMBOLS continued

ABBREVIATIONS

RCT	Randomized Control Trial
TSB	Two-Stage Bootstrap
US	United States
WTP	Willingness to Pay

SYMBOLS

Δ Difference

λ Willingness to Pay Amount

DECLARATION OF ACADEMIC ACHIEVEMENT

Meghann Lindsey Gregg extrapolated the resource utilization and effect data from the Hutterite Influenza Prevention Study data on file and gathered unit cost information on resource utilization. Cost and effect data was inputted into Excel statistical software and a two-stage bootstrap with shrinkage was created as outlined in two papers by Gomes et al. 2011 (1,2). Dr. Robert Hopkins assisted in interpretation of shrinkage correction equations and Professor Gordon Blackhouse provided input into the construction of the two-stage bootstrap in Excel. Meghann Lindsey Gregg interpreted two-stage bootstrap results for base case and all sensitivity analyses, calculated outcome measures, and wrote this thesis. All thesis committee members (Professor Ron Goeree, Dr. Mark Loeb, Professor Gordon Blackhouse, and Dr. Larry Lynd) provided valuable feedback during the entire process (planning, construction, trouble-shooting and written reporting).

CHAPTER 1 INTRODUCTION

1. Disease Background

Influenza is caused by a virus that can be classified into three species: A, B and C. Typically there are multiple strains circulating at a time, with the incidence of infection from a strain reaching epidemic levels in the winter months (3). The predominant strains differ each year due to mutations of the circulating viruses. Minor mutations, from antigenic drifts, produce variation in circulating strains in all influenza species types and result in usual annual epidemics (4), with attack rates of about 10-20% (5). Strains produced from antigenic drifts are often referred to as infections from seasonal influenza. Large mutations from antigenic shifts in influenza A strains typically result in outbreaks with increased attack rates (50%) and severity (4,5).

Influenza can infect both the upper and lower respiratory tracts (6). Signs and symptoms of infection include muscle aches, fatigue, chills, sinus problems, nasal congestion, headache, sore throat, cough, ear ache or infection, and fever ≥ 38 degrees (5,7). The signs and symptoms of influenza can be severe enough to disable a person so that they cannot perform their usual activities. Influenza can also lead to severe outcomes such as hospitalization or death from primary influenza pneumonia or bacterial pneumonia, which is associated with influenza (4).

It is difficult to precisely measure the incidence of influenza due to a number of factors. For example, not all persons with influenza have signs or symptoms and of those with signs and symptoms not all seek health care services. For those suspected of having influenza who do seek services, few are tested with nasopharyngeal or throat swabs to confirm infection from the virus. Additionally, if influenza is determined by the presence of signs or symptoms this will likely lead to an overestimation of those infected who seek care, as other respiratory viruses circulate during influenza season that produce similar signs and symptoms and are clinically indistinguishably from influenza (8).

Often the impact of influenza is estimated by measuring the incidence of severe outcomes such as death or hospitalizations due to influenza. For example in the United States (US) in 2004 seasonal influenza accounted for 21,000 hospitalizations (9) and average number of deaths in the US due to seasonal influenza epidemics are estimated to be 47,800 (10). Typically strains produced from antigenic shifts in influenza A result in more infections and more sever outcomes such as death, however this is not always the case. For example, deaths in the US from antigenic shift strains were estimated to be 12,000 in 2009, 86,000 in 1968, 150,600 in 1957, and 1,272,300 in 1918(10).

Those who experience severe outcomes most frequently are vulnerable groups, for example people with compromised immune systems and people who are unable to mount a strong antibody response to the virus. The elderly (≥65 years) are considered a vulnerable group, though in some instances this is not

always the case. For example the mean age of death from 1979-2001 due to influenza was 75.7 years; however, in 1918 the mean age of death was 27.2 years and in 2009 it was 37.4 years (10)(11). The latter two estimates were from years when an antigenic shift strain was present.

The incidence of influenza is difficult to measure and it is equally as difficult to predict how and who it will impact from year to year, particularly with the emergence of an antigenic shift strain. Influenza does have the potential to be quite devastating, as most notably seen with the 1918 pandemic, and we therefore make efforts in our society to lessen the impact of this disease.

2. Prevention of Influenza

To prevent transmission of the virus two main strategies are promoted in Canada; behavioural modification and immunization. Suggested behaviour modification includes hand washing, covering one's mouth if they sneeze or cough, and staying at home if a person feels ill(12). Immunization protects people through inoculating them with a mild or inactive strain of the suspected circulating virus, which stimulates an antibody response, thereby protecting against future infections from a similar virus (13). The World Health Organization tracks influenza strains worldwide and makes predictions about which strains are likely to be present in the upcoming influenza season which informs the recommendations for which strains should be included in vaccines (14). Due to

the changing nature of the influenza virus, immunity, whether due to past infection or vaccination, usually only lasts for one year, therefore vaccination for influenza is suggested to occur each year.

Canada has the ability to supply influenza vaccines for stains produced by antigenic shifts to all Canadians (15), and universal vaccination for seasonal influenza is available in Ontario (16). Vulnerable groups are encouraged by the Public Health Agency of Canada (PHAC) to be vaccinated against influenza. According to the PHAC, vulnerable groups include persons with chronic conditions, for example people with metabolic diseases, cardiac or pulmonary disorders, hemoglobinopathy, anemia, immune-compromising conditions, renal disease and those with conditions that are associated with aspiration and disrupt the management of respiratory secretions. Also considered to be vulnerable are the morbidly obese (BMI>40), children treated long term with acetylsalicylic acid, those in nursing homes or in chronic care facilities, the elderly (≥65 years old), children aged 6-23 months who are healthy, aboriginal people and pregnant women (17).

Though immunization efforts aim to protect the above high-risk groups, it has been demonstrated that direct vaccination efforts may provide inadequate protection for some groups as they are unable to mount an antibody response to vaccination; one such group is the elderly. As shown in a recent systematic review, evidence poorly supports the direct protective effect of vaccination of the

elderly (8). It would appear that current immunization efforts do not protect those who typically suffer the biggest burden from influenza infection.

3. A New Strategy: Vaccinating Healthy Children to Stimulate Herd Effect

To protect vulnerable groups, and particularly the elderly who appear not to benefit from direct vaccination, a strategy of vaccinating healthy school-aged children to stimulate a herd effect has been proposed. Herd effect is an alteration in the incidence of disease in the unimmunized portion of a population produced by the immunization of a segment of the population(18). The theory behind this strategy is that as children are thought to be major proliferators of influenza (11,19), having them vaccinated, a proven strategy in this group that provides a direct protective effect in children (8), will in turn minimize the spread of influenza in a community.

The results of a recent cluster randomized controlled trial (The Hutterite Influenza Prevention Study(7)) strongly supports the validity of this theory and was the impetus for this economic evaluation. To develop an understanding of the previous investigation into this theory a literature review was conducted in November 2011 of PubMed, the Cochrane Collaboration, and the Internet, using Google. References of included studies were also examined to find additional studies. The search yielded seven studies in total (7,20-25). All study types were included provided they examined the effectiveness of vaccinating healthy children

on the children themselves as well the incidence of influenza in the wider community. All publication years were included in the search and only English language studies were reviewed.

All studies showed results in favour of this strategy or uncertain results (no effect). The variation in study results was likely due to differences in the way studies measured the incidence of influenza. For example, most studies measured the incidence of influenza by counting acute respiratory illness, hospitalizations or deaths (20-23). These measures would underestimate the effect of the strategy, as most people infected with influenza do not have such severe outcomes. Another study measured incidence by patient reported influenza, which could either result in an overestimation or underestimation of the incidence (24). This is because influenza does not always produce signs and symptoms (8) so some cases would go unrecorded, and the fact that influenza is indistinguishable from other circulating respiratory viruses that exist during the influenza season (8), therefore relying on patient reporting could result in an overestimation of incidence.

Two of the included studies used laboratory confirmation of influenza to measure the incidence of influenza (7,25). However the age range of the children vaccinated in one study (Hurwitz et al. 2000(25)) was quite narrow (24-60 months) as opposed to the more recent study by Loeb et al. 2010(7) that included children aged 36 months to 15 years. Limiting the age of the children does not allow the full potential of the strategy to be explored.

4. The Hutterite Influenza Prevention Study

The Loeb et al. 2010 study, called the Hutterite Influenza Prevention Study, provided strong evidence in support of a strategy of vaccinating healthy children. The Hutterite Influenza Prevention Study was a three-year multi-centre, blinded, cluster-randomized, controlled trial. It was conducted in 2008-2011 in three Canadian provinces, Alberta, Saskatchewan, and Manitoba. The Hutterite people, a Christian sect who live communally and in rural areas, were the subjects of the study. The Hutterite colonies or communities included in the trial were composed of a number of families and ranged in size from 23 people to 123 people (see *Appendix 1*) (26).

The study included 46 rural communities and 3273 participants, 947 healthy children vaccinated and 2332 unvaccinated other community members. Subjects were similar at baseline (see *Appendix 2*). Entire communities were randomized to be vaccination or non-vaccination communities. The healthy children in vaccination communities were given inactivated trivalent influenza vaccine and in non-vaccinated communities the healthy children were given hepatitis A vaccine. Hepatitis A vaccine was chosen as the control to provide benefit to participants in the control arm. The treatment arm consisted of 22 communities, 1773 subjects, and the control arm consisted of 24 communities, 1500 subjects. All consenting/assenting eligible subjects aged 36 months to 15 years were immunized with one dose if they had been vaccinated for influenza in a previous year and two doses if they were aged ≤9 years and had never before

received a vaccination for influenza. The follow-up period was six months, the duration of the influenza season, and included the vaccinated children as well as other community members.

The Hutterite Influenza Prevention Study accurately estimated the incidence of influenza by using laboratory tests to confirm cases. Study nurses took nasopharyngeal or throat specimens from participants who reported signs or symptoms during follow-up visits.

In the unvaccinated, influenza was confirmed in 39 of 1271 (3.1%) subjects in the treatment arm and 80 of 1055 (7.6%) subjects in the control arm. In all subjects (vaccinated and unvaccinated) influenza was confirmed in 80 of 1773 (4.5%) subjects in the treatment arm and 159 of 1500 (10.6%) subjects in the control arm. The study demonstrated that vaccinating healthy children for influenza reduced the incidence of influenza in unvaccinated community members as well as entire communities.

5. Economic Evaluation: Thesis Aim and Question

It was decided *a priori* that an economic evaluation would be performed using data (economic and clinical) collected during the Hutterite Influenza Prevention Study. Resource utilization was collected at the level of individual subjects via a self-reporting checklist that was given to each household. Study nurses visited each community two times a week for the entire follow-up period to

assess study participants for signs and symptoms of influenza and record all-cause healthcare resource utilization and absenteeism from work and school as indicated in the household checklists.

It is appropriate to conduct an economic evaluation of this trial because of the study design of the trial. For example, resource utilization was collected for each participant and was unbiased as each participant was followed in the same manner regardless of clinical outcome. Also important, it is appropriate to conduct an economic evaluation of this trial because no previous clinical study investigating the vaccination of healthy children has fully captured the effectiveness of the strategy, as indicated above. Furthermore, no economic evaluation currently exists that examines the strategy of vaccinating healthy children and uses laboratory confirmation of influenza cases as a measure of effect.

The resulting economic evaluation, which is the topic of this thesis, estimates the costs of the intervention and control groups in the Hutterite Influenza Prevention Study by applying associated unit costs to resource data collected for each patient in the trial, and analyses the cost and clinical effect measures to calculate cost-effectiveness. This economic evaluation could potentially be of value to decision makers, assisting them with judgements about whether or not this strategy represents good “value for money”, an important question in a resource-scarce environment.

The objective of this study is to determine the cost-effectiveness of an influenza immunization program directed at healthy children, versus not implementing this strategy. The population examined in this evaluation are healthy children aged 36 months to 15 years who were vaccinated in the Hutterite Influenza Prevention Study as well as other community members. Comparators were vaccination strategy directed at healthy children with inactive trivalent influenza vaccine (intervention) and not implementing this strategy, using hepatitis A vaccine as the control. The main outcome measures of this evaluation are mean costs and effects for the treatment and control groups. If dominance does not exist, an incremental cost-effectiveness ratio (dollar per case of influenza averted), and the probability of cost effectiveness were calculated from net monetary benefit statistic. The study type is an economic evaluation, cost-effectiveness analysis.

CHAPTER 2 METHODS

1. Introduction to Methods Chapter

This chapter begins by describing what an economic evaluation is and what it is used for. The three main types of economic evaluations are defined; cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA), and justification is given for the choice of conducting a CEA. The analysis is then framed in terms of the evaluation context, question, target population, comparators, viewpoint, timeframe and analytic horizon.

Next costs and effects are assessed, outlining the rationale for inclusion of inputs, process and sources for collection, as well unit costs are presented. How costs and effects are combined for the CEA is then described as well as a discussion of the appropriate statistical analysis for conducting a CEA of data from a cluster randomized controlled trial. The chosen statistical analysis of costs and effects, a two-stage bootstrap (TSB), is defined and justified and the process of conducting a TSB is detailed. Estimates derived from the TSB will be used to calculate outcome measures, incremental cost-effectiveness ratio and net benefit. These are defined and discussed as well as uncertainty around these measures. Finally, the types of sensitivity analysis are proposed are discussed, one-way sensitivity analysis and multi-way sensitivity analysis (scenario analysis).

2. Economic Evaluation

The purpose of an economic evaluation is to compare the costs and consequences (effects) of alternative strategies (27). In the context of health, strategies can include services, procedures, or programs. The costs included in an economic evaluation vary depending on the viewpoint taken. For example, a third party payer viewpoint will only consider the resources utilized that incur a cost to that payer, such as resources that are reimbursed by that payer, whereas a societal viewpoint can consider all costs to all people/institutions, including third party payer, government, employer, volunteer caregivers, patients et cetera. In taking a societal viewpoint, loss of productivity is considered to be included in the cost of a strategy. To illustrate, if a person were to miss work due to illness, productivity would be considered lost. The consequences included in an economic evaluation can be cases of a particular disease or health outcomes such as disability and death (27).

In an environment with limited resources, an economic evaluation can be a very useful tool that can contribute to the decision making process. It does this by contributing to existing pieces of information on a strategy, such as efficacy, effectiveness and availability relating to the specific strategy (27). Economic evaluations help determine if one strategy, compared to another, or others, is a good “value for money”, through a measurement of the additional cost per unit of outcome or benefit (27).

There are three types of economic evaluations most commonly used today: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). They differ primarily in the way the effect is measured and valued. For example, CEA measures the effect outcome in natural units, such as number of cases of a disease, CUA uses a broader utility measure that allows for quantification of the morbidity and mortality impact of the outcome by the measurement of the quality adjusted life years (QALYs), and CBA measures effect in terms of a monetary value.

This economic evaluation was based on data collected from a trial, the Hutterite Influenza Prevention Study. It was decided that a CEA would be conducted because natural units, cases of influenza, was the most appropriate measure of effect as none of the participants followed had severe outcomes directly related to influenza infection. Additionally, placing a significance value on influenza infection as done in a CUA, would have produced a very small QALY as signs and symptoms of influenza infection last from 2 to 5 days (28). Using QALY is not the optimal tool for short-term illnesses as having such a small QALY is not very useful for comparing strategies. Also, using cases of influenza is simple to understand for decision makers and allows for comparison of other influenza prevention programs, including those that are outside of the health sector (29).

3. Framing the Analysis

3.1. Study Question

What is the cost-effectiveness of an influenza immunization strategy that vaccinates healthy children, aged 36 months to 15 years, on community herd immunity, measured by cases of influenza, versus not implementing this strategy?

3.2. Target Population

The target population of this economic evaluation is all members of the communities. Though the immunization strategy directly vaccinates only healthy children, the benefits of this extend beyond the children and to the community at large. Additionally, entire communities were included in follow-up of the Hutterite Influenza Prevention Study.

3.3. Comparators

The intervention is an influenza immunization strategy that targets healthy children for vaccination and measures the effect (incidence of influenza) on all community members, both vaccinated and unvaccinated. The comparator is not implementing this strategy. In the trial, those children in communities randomized to the treatment arm received inactive trivalent influenza vaccine VAXIGRIP produced by Sanofi Pasteur and those in the control arm received hepatitis A

vaccine, AVAXIM also produced by Sanofi Pasteur (30). Hepatitis A vaccine was chosen so that subjects would receive a benefit from participation regardless of which arm they were in (30). This economic evaluation, as well as the trial on which it is based, examines the strategy, not the effectiveness of the vaccine in children, which has well established (8).

One may ask how useful it is to decision makers to consider an economic evaluation of an immunization strategy against no strategy. In fact it is quite useful when one considers the environment of the Hutterite Influenza Prevention Study, which is similar to the present environment in Ontario in regards to efforts for protecting the population against influenza. For instance, there were a number of participants who received influenza vaccination in each arm that were not healthy children. These were 'at-risk' individuals who decided to be vaccinated against influenza from other healthcare professionals, not study nurses. Ethically one could not discourage a person from being immunized due to their participation in the study. These other persons vaccinated were about equal in each arm. They amounted to 172 persons in the treatment arm (9.7%) and 122 persons in the control arm (11.6%) (7). These percentages are not greatly dissimilar from Ontario 1996/1997 estimates of influenza immunization uptake and to some provincial/territorial estimates for 2005 (31). As well Hutterite communities are similar to other Canadian communities as members receive the messaging from National and Provincial governments and institutions about

behaviour modification to prevent influenza. Both of these points make the environment of the trial at baseline similar to the current Ontario environment.

3.4. Viewpoint

The viewpoint of this economic evaluation is societal, that is all costs and all consequences to all people. However, the viewpoint is constrained to the data collected in the trial. Therefore the viewpoint is a limited societal perspective.

3.5. Timeframe, Analytic Horizon

The timeframe and analytic horizon combined is six months, which is the duration of the follow-up period of the trial and of the influenza season. All relevant effects and costs occurred during this time period and ceased after the influenza season as the virus generally no longer causes infection and immunity will not extend to the next influenza season due to mutation of the virus.

3.6. Discounting

There is no discounting of costs or effects due to the short analytic horizon (six months).

4. Assessment of Costs

4.1. Included Cost Items

Costs included in an economic evaluation are not just the costs incurred by a certain strategy or from the consequence of a strategy, but the use of a resource that is being consumed and unable to be used for another purpose. The costs in an economic evaluation are monetary representations of resource utilization. As mentioned above, the viewpoint of this economic evaluation is societal; however, the costs that are incorporated are constrained to the data collected in the trial. The trial collected resource utilization during vaccination and follow-up. Data collected on resource utilization associated with the vaccination period included the cost of the vaccine, and the cost of nurses to administer the vaccine. Facility rental was added to the list of resources utilized. Even though facility rental was no explicitly recorded during the trial, space in each community was provided “free of charge” and this space could have been utilized for a different purpose. The cost of a space to provide vaccinations was also included because in most circumstances a community would charge for space to be rented and even if offered for free there is a value attached to a space that is lost when the space is used for another purpose.

Data collected on resource utilization during follow-up included doctor visits, hospital admissions, hospital visits, emergency room (ER) visits, antimicrobial prescription, and absenteeism from school or work. The utilization of

these resources was included regardless of the reason for utilization, i.e. these resources were counted even if they were not utilized due to influenza infection.

Protocol driven costs are not included in the list of resource utilization items. Protocol driven costs are the costs associated with doing the trial (32), and in this instance costs excluded were those associated with preserving blinding of the comparison strategy; control vaccine, nurse time to administer control vaccine and facility rental to administer control vaccine.

4.2. Calculation of Unit Costs

Costing information was collected for the above items from government reports, local suppliers, peer-reviewed articles, Internet searches, and study data on file from the Hutterite Influenza Prevention Study. Details of costing for each resource is described below and summarized in *Table 1*. Unit costs for resources were estimated for the year 2011 and are in Canadian dollars. There were missing data for one cost item, antimicrobial prescription. Details of the method used to handle the missing data is described below under this item's costing description.

4.3. Vaccination Administration Costs Per Vaccination, Treatment Group

The costs of administering the vaccine to the treatment group included the cost of the vaccine, the cost of needles, nursing staff and facility rental. In the treatment arm 502 children were vaccinated. 223 children received one dose as they had been vaccinated before, and 279 children received two doses because they were aged ≤9 years old and had never before been vaccinated for influenza. This resulted in 781 doses of the influenza vaccine being administered in the treatment arm.

4.4. Vaccine

The vaccine used in the treatment arm was the influenza vaccine VAXIGRIP produced by Sanofi Pasteur. A community pharmacy was approached in Hamilton, Ontario and the wholesale price for the vaccine was obtained; $8.77 per 0.5 ml dose.

4.5. Needles

The cost of VAXIGRIP includes a syringe but not a needle. Inactivated influenza vaccine is an intramuscular injection administered with a 1” needle length for children 28 days to 18 years of age (33). A 22-25 gauge needle should be used for vaccines (33). Needle costs were estimated from a Canadian online

medical supply store, selling Nipro 25 gauge 1" hypodermic needles for $6.49 for a box of 100 (34). No tax is included as the province of Alberta, where the distributer is located, does not have sales tax (35). As this price is subject to purchasing 100 needles, the number of needles needed for the treatment arm is rounded up to the closest 100 (781 to 800). Needles are shipped in via Canada Post and shipping is estimated to cost $19.78 (36) for 8 boxes of 100 needles each for a weight of 10 lbs. with dimensions 12 x 10 x 5 inches, shipped regular parcel from Calgary Alberta, the location of the medical supply store, to Hamilton Ontario. Unit cost per needle is $0.09 and is calculated as follows:

$6.49 x 8 boxes = $51.92

$51.92 + $19.78 = $71.70

$71.47/781 doses= 0.09151088348, rounded to 0.09

4.6. Nursing Staff

Two nurses were present during each vaccination in case a subject had an adverse event. Study nurses were paid $37.50 per hour, and the total amount of time nurses worked administering both the treatment and the control was 1,473.46 hours (26). To estimate the nursing time for one vaccination, the total amount of time nurses worked for the first year of the trial was divided by the total number of vaccination doses administered for both arms (1,473.46/1,569). The quotient is .94 hours (56.4 minutes, 0.94 x 60) per vaccination. The cost of nursing staff per one dose is estimated at $70.50 (0.94 x 75, two nurses at

$37.50 per hour). Nursing time included administering vaccination and travel time to communities. Hutterite communities are in rural areas and those included in the trial were within a 150 kilometer distance from designated cities or towns so that nursing staff could travel to the communities two times per week for follow-up.

4.7. Facility

Vaccines were administered in Hutterite communities in the community kitchen (26). As Hutterite colonies are in rural areas and those included in the study were within a 150 km radius of a city, these two criteria were considered when choosing a suitable estimate to inform cost of renting a space. A search on Google was conducted and yielded a suitable location in Innisfil Ontario, a rural community located 20.09km(37) from the city of Barrie. The location was a hall space in St. Paul's Church that rented for $358 a day, including insurance (38). Daily rental is assumed to be for 8 hours. To estimate cost of facility rental for one vaccination, the hourly rate of rental was calculated ($358/8 hours=44.75 per one hour) and then multiplied by the time it takes for one vaccination (0.94 hours/2, time it takes for two nurses to administer one dose/2 nurses) for a product of $21.03 (44.75 x 0.47 hours). The amount of time estimated to administer one vaccination was the quotient of the nursing time for two nurses to administer a vaccination divided by 2 (0.94/2). The estimate of $21.03 is likely an underestimation for this trial as this estimate assumes that all doses were

administered at the same location and in the same short time period. This was not the case as there were 22 treatment communities, and for those who required a second dose it would have been administered four weeks later. Additionally, rental space is usually reserved by the day or half-day; therefore even though a team of nurses may only require a space for 6 hours, the cost for a full-day would be charged as the space could not be used for another activity.

4.8. Cost of One Dose of Influenza Vaccine

The total cost of one vaccination dose is $100.39, the sum of the vaccine cost ($8.77), needle cost ($0.09), nursing cost ($70.50) and facility rental cost ($21.03).

4.9. Follow-up Period Costs: Treatment and Control Group

Follow-up costs included doctor's visits, hospital admissions, hospital visits, ER visits, antimicrobial prescriptions, and absenteeism from work or school.

4.10. Doctor visit

Cost of a doctor visit is $77.20 and was obtained from the Ontario Health Insurance Plan (OHIP) schedule of benefits 2011 for a general assessment (39).

4.11. Hospital Admission

Costs for hospital admission were calculated from the Ontario Case Cost Initiative (OCCI) for acute inpatient influenza upper respiratory tract infection 2009-2010(40). Cost per average hospital admission was $14,641.68 for 8 days. To calculate a per day amount the average cost was divided by 8, the product of this was $1830.21. This amount was converted from 2009 dollars to 2011 dollars with the Bank of Canada inflation calculator (41), for an estimated daily cost $1,916.30 for hospital admission.

4.12. Hospital Visit

Cost of a hospital visit was estimated to be $157.00 for adults >16 years old, and $165.50 for children ≤16 years old. Hospital visits were assumed to be visits to hospital clinic to see a respirologist. Costs were obtained from the OHIP schedule of benefits for respirology disease consultation (39).

4.13. Emergency Room Visit

Cost of emergency room (ER) visits was estimated to be $244.68. This amount was determined by taking the average cost of ER physician service from the OHIP schedule of benefits, $55.175 (39) and adding estimated non-physician costs to the hospital, $181.00 (estimated from Sander et al. 2010(16)), converted from 2009 dollars to 2011 dollars, $189.51 (41).

4.14. Antimicrobial Prescription

No antivirals were prescribed to study participants, only antibiotics were prescribed. Antimicrobial course was estimated by taking the average antimicrobial course for all participants per arm. The average was estimated to be eight days in each arm. Guidelines suggest levofloxcin for the treatment of secondary bacterial infections (42). Adult dosing >16 years of age is 500mg per day and dosing for children ≤16 years of age the maximum amount is 250mg per day (maximum assumed) (42).

There were missing data for the number of days antimicrobials were prescribed for some subjects in each arm. Missing data was contended with by assuming that all subjects who were prescribed antimicrobials were prescribed the average course (eight days).

4.15. Absenteeism from Work or School

Resource costs associated with absenteeism from work or school were estimated as the amount of wage lost per a day of work. Wages for one day of work were estimated by taking the average hourly wage in 2011 (43) and multiplying it by eight for a daily estimate ($23.39 x 8 = 187.12). The same unit cost was used for missing a day of school and missing a day of work. Even though children do not lose pay when they miss a day of school, it was assumed that an adult would alter their schedule to care for the child.

Table 1: Unit Costs

Category	Unit Cost 2011 CAD	Source
Vaccination Costs (per dose)		
Vaccine, VAXIGRIP	$8.77	Hamilton Ontario Pharmacy
Needle	$0.09	Vereburn Medical Supply, shipping Canada Post
Nurse (to administer vaccine, 2 nurses required)	$70.50	Singh, Hutterite Influenza Prevention Study-data on file
Facility (to administer vaccine)	$21.03	St Paul Church, Innisfil Ontario
Total Vaccination cost	$100.39/dose	
Follow-up Costs		
Dr. Visit (GP)	$77.20	OHIP Schedule of Benefits, general assessment
Hospital admission	$1,916.30	OCCI, cost per day, acute inpatient influenza, adjusted to 2011
Hospital visit, adult, >16 years	$157.00	OHIP Schedule of Benefits, respirology disease consultation
Hospital visit, adult, ≤16 years	$165.50	
ER visit	$244.68	OHIP Schedule of Benefits, average ER physician service (55.175) plus non-physician service costs (Sander et al. 2010) 2009 adjusted to 2011
Antimicrobial		Average course 8 days, Loeb, Hutterite Influenza Prevention Study-data on file, levofloxacin $1.2038/250mg dose, Ontario Public Drug Programs e-formulary, dosing Up To Date
Adult (>15) 500/day	$19.21	
Children (≤15) 250/day	$9.63	
Value of lost workday/school day	$187.12	Statistics Canada, Average Hourly Wage x 8

5. Assessment of Effects

The effect outcome for this economic evaluation was cases of seasonal influenza. The influenza vaccine recommended for the influenza season 2008-2009 included two influenza A strains (A/Brisbane/59/2007(H1N1)-like and A/Uruguay/716/2007(H3N2)-like) and one influenza strain (B/Florida/4/2006) (44). In the Hutterite Influenza Prevention Study there were 80 cases of influenza in the treatment arm and 159 cases in the control arm. Cases were confirmed through laboratory testing, from nasopharyngeal or throat specimens (Polymerase chain reaction, PCR). PCR testing is estimated to have 100% specificity and 95% sensitivity for detecting influenza (30). When results of PCR are positive for influenza the specimen is then prepared for viral culture that determines the type of influenza strain.

6. Cost Effectiveness Analysis

Objectives of conducting this CEA are to estimate the average costs and average effects per arm and if relevant, the incremental cost-effectiveness ratio, and net monetary benefit statistic.

7. Estimating Average Costs and Average Effects

This CEA is based on trial data from a cluster randomized controlled trial (CRT). The unit of randomization in a CRT is an entire group (cluster), in the case of Hutterite Influenza Prevention Study and this CEA the unit of randomization was entire communities. Three criteria must be satisfied in the analysis stage of a CEA of a CRT to ensure accurate estimates are produced; adequate sample size, the recognition of clustering in regards to both costs and effects, and correlation between cluster level and individual level costs and effects (1).

Adequate sample size has been satisfied as the investigators of the CRT accounted for clustering in the sample size calculation. Recognition of clustering and correlation of costs and effects are satisfied when appropriate methods are used to estimate cost-effectiveness in CRTs. Over 90% of published CEAs on CRTs use inappropriate statistical methods (1). Standard methods used for analysis of randomized controlled trials (RCT) should not be used as they ignore clustering which could lead to an underestimation of the statistical uncertainty and produce inaccurate point estimates (1). Additionally, if cluster sizes are imbalanced (unequal number of subjects per cluster), using a method that ignores clustering will result in biased estimates (1). As well, the use of statistical methods tailored simply to test and summarize cluster level data lack the ability to address the correlation between individual cost and effects(1).

Establishing appropriate methods for conducting CEA of CRT is still in its infancy, with the publication of the first known paper assessing the

methodological quality of proposed methods for CEA of CRTs being in May 2011(1). This paper suggests three appropriate statistical methods that one should use when conducting a CEA on CRTs, each recognizing clustering and the correlation of costs and effects. They are, multilevel modelling (MLM), generalized estimating equations (GEE), and the two-stage nonparametric bootstrap (TSB)(1).

TSB was chosen for this CEA because a shrinkage estimator can be added to the method that takes into consideration imbalanced cluster sizes, which was the case in the Hutterite Influenza Prevention Study (see *Appendix 1* for cluster sizes for each arm). Adding a shrinkage estimator is recommended to "correct for possible overestimation of the variance"(2). The only limitation of the TSB is that if the number of clusters is too few (<20) asymptotics will not hold(1). This is not a limitation for the use of this method with the Hutterite Influenza Prevention Study data as the treatment arm had 22 clusters and the control had 24.

The TSB resamples with replacement clusters and subsequently individuals. Cost and effects are resampled as pairs, thereby recognizing correlation. Outlined below are the seven steps to constructing a TSB with shrinkage correction used in this thesis. These steps were adapted from appendix 2, algorithm 2, in Gomes et al. 2011(2)(see *Appendix 3*), so that TSB could be constructed in Excel.

7.1. Steps to Constructing a Two-Stage Bootstrap

I. Shrunken means are calculated for each cost ($\hat{x}_j^c$) and effect ($\hat{x}_j^e$) for each cluster, in each arm.

$$\hat{x}_j^c = \left(c\bar{\bar{X}}_k{}^c\right) + ((1 - c^c)\bar{x}_j{}^c)$$

$$j = cluster$$

$$k = treatment\ arm$$

$$\bar{\bar{X}} = grand\ mean\ of\ clusters\ in\ arm$$

$$c = 1 - \sqrt{A}$$

$$A = \frac{Mk}{Mk - 1} - \frac{SS_w}{b(b-1)SS_B}$$

$$Mk = Number\ of\ clusters\ in\ treatment\ arm$$

$$SS_w = within - sum\ of\ squares$$

$$b = cluster\ size$$

$$SS_B = between - sum\ of\ squares$$

II. Standardized individual level residuals are calculated for cost and effect for all subjects.

$$Individual\ residual = \frac{i^c - \bar{x}_j{}^c}{\sqrt{1 - \bar{n}^{-1}}}$$

$$i = inividual\ subject$$

$$\bar{n} = average\ cluster\ size\ in\ arm$$

III. Shrunken means and residuals are added together to create a new cost and effect pair for each individual.

IV. Clusters are randomly sampled with replacement in each arm. Sampling with replacement means the same cluster can be sampled more than once. For example, in the treatment arm there are 22 clusters. Numbers identifying each cluster (1-22), are sampled to comprise a frame of a synthetic treatment arm of 22 randomly selected clusters.

V. Individual pairs of cost and effect (shrunken means plus residuals) are randomly sampled with replacement within each cluster and attached to the clusters of the synthetic arms. For example, if in the synthetic treatment arm frame randomly chose cluster 4 of the treatment arm which has 38 subjects, then those 38 subjects' cost and effect pairs would be randomly sampled with replacement to construct the synthetic new cluster.

VI. The mean cost and effect of each synthetic cluster is calculated to compute the grand mean for each arm.

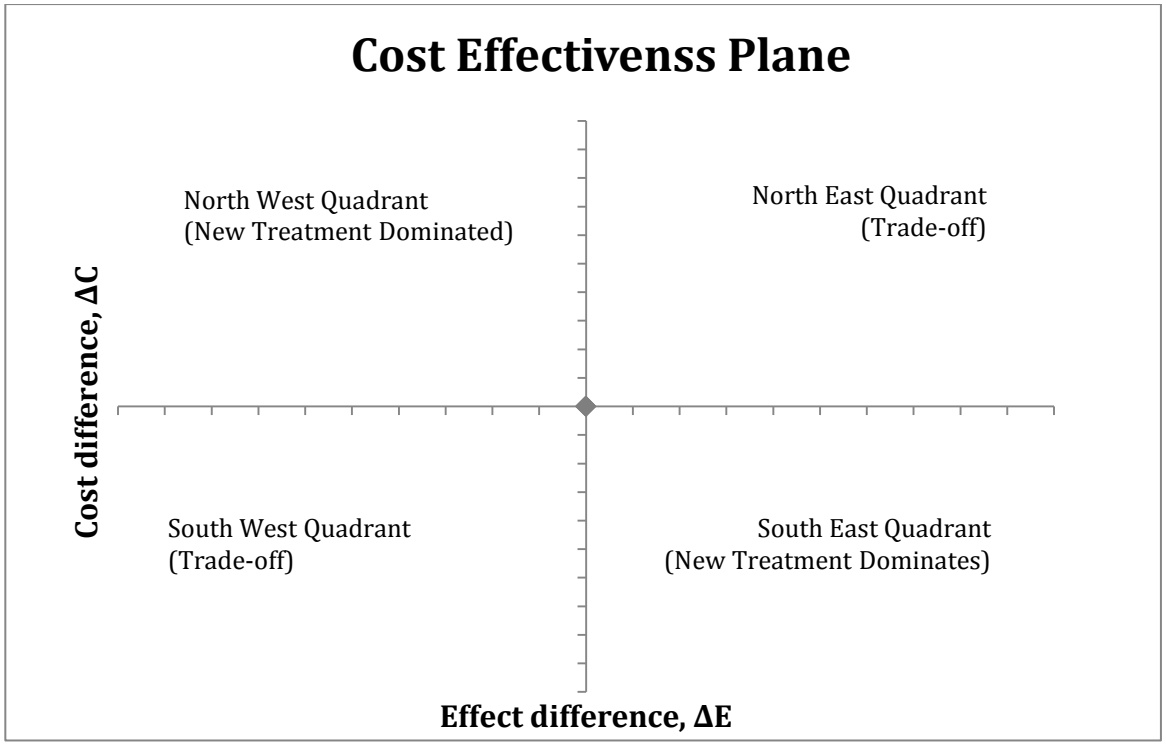
VII. Steps 4 to 6 are repeated 1000 times to construct the bootstrap sample.

8. Analysing Results of TSB

The TSB will produce an estimate of the individual average cost and average effect for the treatment and the control strategy 1000 times in the final

sample. Next effect will first be converted from cases of influenza to influenza-free cases (1- cases of influenza). This is done because in order for cost-effectiveness to be plotted and interpreted correctly on a cost effectiveness plane effect must be a potential benefit. Cost-effectiveness is then determined by considering and plotting the average of these estimates on the cost effectiveness plane *(Figure 1*).

Figure 1: Cost Effectiveness Plane



Adapted from Briggs, Claxton and Sculpher 2006(45)

At the intersection of the vertical effect axis and the horizontal cost axis lies the comparator. The difference in cost and effect of the (treatment)

intervention versus the (control) comparator is plotted on the CEP in relation to the comparator. If the intervention is less costly and more effective it will lie in the South East quadrant and is then said to dominate the comparator. If the intervention is more costly and less effective than the comparator it will fall into the North West corner and then the intervention is said to be dominated by the comparator. Interventions that fall into either of these two quadrants make for easier decision making; however, if the intervention falls into the North East quadrant (intervention more costly and more effective than comparator) or the South West quadrant (intervention less costly and less effective than the comparator) then a trade-off between cost and effects must be considered. This is done by calculating the incremental cost effectiveness ratio (ICER) for the intervention versus the comparator. This is calculated by taking the difference in cost between the two strategies and dividing it by the difference in effect between the two strategies ($ICER=\Delta Cost/\Delta Effect$).

9. ICER and Net Benefit

If an ICER is calculated this will result in an ICER representing the incremental cost per case of influenza averted. The ICER will be calculated by taking the quotient of the difference in cost divided by the difference in effect, which is calculated from the average of the 1000 cost and effect pairs from each arm. Deciding if this additional cost per case of influenza averted is cost-effective

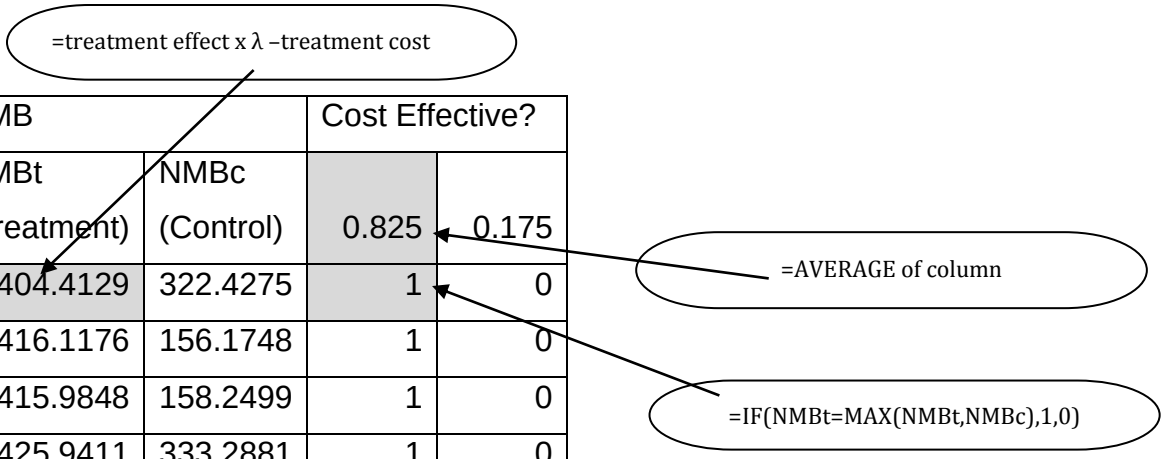
is dependent on the decision maker's willingness-to-pay (WTP). Typically for an ICER to be useful the decision maker has to have some idea beforehand how much they are willing to pay (threshold). If the ICER is less than the threshold the strategy can be considered cost-effective.

To communicate the measure of uncertainty of the ICER estimate a confidence interval (CI) can be calculated. The data produced by the TSB gives the opportunity to easily construct a CI. This is done by ordering from lowest to highest the ICERs for each sample in the final 1000 bootstrap sample and then taking the 25^{th} ICER number for the lower bound and the 975^{th} ICER number for the upper bound. One difficulty that can arise with the estimation of a CI around an ICER is when negative ratios are included in the CI. If negative results are present this means that ICERs have fallen into more than one quadrant on the CEP, which leads to un-interpretable results.

Another way of expressing the uncertainty around cost-effectiveness results is with a cost-effectiveness acceptability curve (CEAC). A CEAC is a visual representation of the probability of cost-effectiveness of the treatment strategy relative to the control. CEACs are informed by the net monetary benefit statistic (NMB). NMB is calculated by multiplying the effect estimate from the TSB results by a WTP threshold (λ) and subtracting cost ((effect x λ)-cost). At any given WTP the comparator with the highest NMB statistic is considered the most cost effective.

NMB is calculated for each one of the 1000 final bootstrap cost and effect pairs in each arm. To create the CEAC in Excel two cost-effectiveness columns are created beside each pair of NMB statistics (pair includes the NMB from the treatment group and from the control) and an 'IF' statement is inserted in the first column commanding that if the treatment has the highest NMB then a 1 is inserted in the column and if the treatment does not have the higher NMB then 0 is inserted. This is done for the next column over as well but for replacing the treatment with control. Then each cell in each cost-effectiveness column is added and the average is determined (see *Figure 2*). This average communicates the probability of each arm being cost-effective at the λ used to create the column NMBs. A Macro is then written and implemented in Excel which creates these NMB statistics and average probability of cost-effectiveness for a variety of λ amounts (see *Figure 3*). The results of this can then be plotted graphically as a CEAC, whereby it is straightforward to determine which strategy is more likely to be cost-effectives at any λ amount.

Figure 2: Calculating Net Monetary Benefit Statistic and Probability of Cost Effectiveness



	NMB		Cost Effective?	
	NMBt (Treatment)	NMBc (Control)	0.825	0.175
1	404.4129	322.4275	1	0
2	416.1176	156.1748	1	0
3	415.9848	158.2499	1	0
4	425.9411	333.2881	1	0
5	419.9861	369.7248	1	0
6	415.4144	392.7534	1	0
7	425.8344	153.0976	1	0
8	418.2208	248.8782	1	0
9	386.6123	434.2025	0	1
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
1000	421.1074	426.7432	0	1

Figure 3: Constructing a Table to Inform a Cost Effectiveness Acceptability Curve

λ	treatment	control
0	0.029	0.971
100	0.412	0.588
200	0.656	0.344
300	0.756	0.244
400	0.789	0.211
.	.	.
.	.	.
.	.	.

NMB is calculated for each cost and effect pair in each arm dependent on the λ. Then the average of the cost-effectiveness 'IF' statement is inputted into this table and a CEAC is generated from this table.

10. Sensitivity Analysis

Uncertainty around the base case estimates was explored by varying unit costs in a one-way sensitivity analysis and by varying multiple cost inputs in a multi-way analysis (scenario analyses).

Found below are estimates for input variations for one-way and multi-way analysis and the justification and sources of choices. Costing of resources consumed during the trial was determined from a number of sources including study data on file, a local pharmacy, government sources, published studies, and online stores and services. The cost and effect units that will inform the calculations, which in turn will determine the inputs in the TSB, were determined

to be either fixed or uncertain. Units were designated as fixed if they were judged to be precise estimates and uncertain if they were not.

Fixed units included effect (laboratory confirmed presence of influenza), and costs (vaccine, doctor visit, hospital visit, emergency room visit, and antimicrobial prescription). The effect unit is considered precise due to the use of two laboratory tests to confirm influenza and their high diagnostic accuracy (see above, assessment of effects). Vaccine cost was considered precise because of the source of costing, a local pharmacy. Doctor visit, hospital visit, emergency room visit, and antimicrobial prescription costs were judged to be precise, due to the sources of their costing (OHIP schedule of benefits(39), Ontario Public Drug Programs e-formulary(46)) and as such their costs do not vary across the province, with the exception of non-physician service costs included in the emergency room estimate. This was not explored in the sensitivity analysis as it was assumed this cost was a good estimate(47) and if varied it would only produce a small impact on the overall study results.

The following cost units were considered uncertain; needle, nurse, facility, hospital admission, value of lost workday/school day. Needle cost was considered uncertain as this cost varies depending on where needles are purchased. Nurse wages vary depending on how experienced the nurse is, and facility costs vary depending on location. Hospital admission costs vary depending on reason for admission, which in turn affects duration and resources consumed (doctor time, nurse time, tests, surgeries et cetera). Value of lost work

or school day varies depending on a person's wage. The uncertainty surrounding these costs will be handled by conducting a one-way sensitivity analysis and a scenario analysis.

11. One Way Sensitivity Analysis

Each uncertain cost input will be varied one at a time to determine if there is an impact on the CEA results. Outlined below are the alternatives for each cost variable and their sources. A summary can also be found in *Table 2*.

11.1. Needles

All needle costs are from Cascade Healthcare Solutions. Cascade Healthcare Solutions ship with UPS or FED Ex (48). Monoject Hypodermic Needles w/ Poly Hub, manufactured by Kendall has a 25 gauge x 1 inch needle in pack of 100 for $11.74(49). There were 781 doses administered to the treatment arm, therefore 8 boxes would be purchased ($93.92, 8 x 11.74). There is no tax charged, and shipping cost is $20 to Hamilton, Ontario, Canada as calculated on the company's website(50) for a total of $113.92 USD. When converted to Canadian dollars the total is $113.17(41). Price per needle per dose is estimated at $0.14 (113.17/781).

An additional needle cost was estimated by calculating the midpoint between the base case and sensitivity analysis estimate. Price per needle per dose is estimated at $0.12 (0.09/0.14, rounded).

11.2. Nurse

A range of full-time registered nurse hourly rates (not including premiums) was gathered from the Ontario Nurses' Association website(51). Three hourly wages were chosen, a starting wage, $29.36, a 5 year wage, $35.15, and a 25 year wage, $42.44. Each wage was multiplied by two, to reflect that two nurses are required to be available during each vaccination, and the product was then multiplied by the amount of time it takes for one vaccination (0.94 hours). The results are as follows.

Starting nurse, $55.20 ((29.36 x 2)(0.94)), rounded

5 year nurse, $66.08 ((35.15 x 2)(0.94)), rounded

25 year nurse, $79.79 ((42.44 x 2)(0.94)), rounded

11.3. Facility

The uncertainty around the base case estimate for cost of facility rental was explored by varying rental cost. A Google search was conducted to identify halls for rent in rural communities in Ontario, that were <150km from a city. Three variations on cost of rental were calculated from three locations. Estimates were

calculated in the same fashion as the base case; the hourly rate of rental was calculated (rental cost per day/8 hours) and then multiplied by the time it takes for one vaccination (0.47 hours (0.94 hours/2, time it takes for two nurses to administer one dose/2 nurses)). The three variations are as follows:

1. $35.25 cost of rental space per one vaccination. Calculated: $600 rental cost per day/8 = $75 an hour. $75 x 0.47 = $35.25. Estimated from St. Mark's Anglican Church(52), Niagara on the Lake, a rural community 28.4km from Niagara Falls(37).
2. $17.62 cost of rental space per one vaccination. Calculated: $300 rental cost per day/8 = $37.50 an hour. $37.50 x 0.47 = $17.62, rounded. Estimated from Royal Canadian Legion Branch 459(53) in Stouffville, Ontario, a rural community, 47.9km from Toronto(37).
3. $5.88 cost of rental space per one vaccination. Calculated: $100 rental cost per day/8 = $12.50 an hour. $12.50 x 0.47 = $5.88, rounded. Estimated from Royal Canadian Legion Branch 197(54) in Acton, Ontario, a rural community 71.1 km from Toronto(37).

11.4. Hospital Admission

The varying costs for hospital admission are $500, $1000, and $1500 per day. Costs were determined by seeking expert opinion; Gordon Blackhouse, Health Economist and Assistant Professor in the Department of Clinical Epidemiology and Biostatistics at McMaster University(47).

11.5. Absenteeism

Absenteeism was varied by inputting the highest average wage for Canada in January 2012 multiplied by eight ($37.04 x 8 = $296.32), and the lowest average wage for Canada in January 2012 multiplied by eight ($15.58 x 8 = $124.64)(43).

Table 2: Cost Inputs, Sensitivity Analysis

Category	Base Case	Variation	Source
Vaccination Costs (per dose) Vaccine, VAXIGRIP	$8.77	FIXED	Hamilton Ontario Pharmacy
Needle	$0.09		Vereburn Medical Supply
		$0.14	Cascade Healthcare Solutions
		$0.12	Midpoint Estimate
Nurse (to administer vaccine, 2 nurses required)	$70.50		Hutterite Influenza Prevention Study, data on file
		$55.20	Ontario Nurses' Association
		$66.08	Ontario Nurses' Association
		$79.79	Ontario Nurses' Association
Facility (to administer vaccine)	$21.03		St Paul Church, Innisfil Ontario
		$35.25	St. Mark's Church, NOTL
		$17.62	Canadian Legion, Stouffville
		$5.88	Canadian Legion, Acton
Total Vaccination cost	$100.39/dose		
Follow-up Costs Dr. Visit (GP)	$77.20	FIXED	OHIP Schedule of Benefits, general assessment
Hospital admission	$1,916.30		OCCI acute influenza per day
		$500	Expert Opinion
		$1000	Expert Opinion
		$1500	Expert Opinion
Hospital visit, adult, >16 years	$157.00	FIXED	OHIP Schedule of Benefits, respirology disease consultation
Hospital visit, adult, ≤16 years	$165.50	FIXED	
ER visit	$244.68	FIXED	OHIP Schedule of Benefits, average ER physician service (55.175) plus non-physician service costs (Sander et al.2010) 2009 adjusted to 2011
Antimicrobial			Average course 8 days, Loeb, Hutterite Influenza Prevention Study-data on file, levofloxacin $1.2038/250mg dose, Ontario Public Drug Programs e-formulary, dosing Up To Date
Adult (>15) 500/day	$19.21	FIXED	
Children (≤15) 250/day	$9.63	FIXED	
Value of lost workday/school day	$187.12		Statistics Canada Average Hourly Wage x 8
		$296.32	Statistics Canada Highest Hourly Wage x 8
		$124.64	Statistics Canada Lowest Hourly Wage x 8

12. Scenario Analysis

As the overall uncertainty in the results may be dependent on the combined variability in several costs, a scenario analysis was also conducted. Three scenarios were constructed to represent potential multi-way analyses. One is an ‘average case’ scenario, which includes the average cost of each uncertain cost input. Average cost was calculated by taking the sum of all estimates (alternatives and base case) and dividing by the total number of estimates. A ‘best case’ scenario was constructed which used the lowest cost for each uncertain cost input. A ‘worst case’ scenario was constructed using the highest cost for each uncertain cost input. Each of the three scenarios will be used in the TSB and if relevant an ICER and NMB will be constructed. A summary of the inputs selected for the three scenarios can be found in *Table 3*.

Table 3: Scenario Analysis Inputs

Cost Input	Average Guess	Source	Best Case	Source	Worst Case	Source
Needle	0.12	average	.09	Vereburn Medical Supply	.14	Cascade Healthcare Solutions
Nurse	67.89	average	55.20	Ontario Nurses' Association	79.79	Ontario Nurses' Association
Facility	19.95	average	5.88	Canadian Legion, Acton	35.25	St. Mark's Church, NOTL
Hospital Admission	1229.08	average	500	Expert Opinion	1916.30	OCCI
Absenteeism	202.69	average	124.64	Statistics Canada Lowest Hourly Wage x 8	296.32	Statistics Canada Highest Hourly Wage x 8

CHAPTER 3 RESULTS

The total effect in the treatment arm was 80 cases of influenza in 1773 subjects (4.5%) and 159 cases of influenza in 1500 subjects (10.6%) in the control arm. Total costs were $107,600.28 for the treatment arm and $70,246.18 for the control arm. Vaccination costs accounted for $78,404.59 in the treatment arm. Further description of the breakdown of costs in the treatment and control arms can be found in *Table 4.*

Table 4: Breakdown of Costs in Treatment and Control Arms

	TREATMENT			**CONTROL**	
	Number (Number of subjects)	*Cost, $*		*Number (Number of subjects)*	*Cost, $*
Vaccination	781 doses (502)	78,404.59 (Nurse: 55,060.50)		-	-
Dr. Visit	109 visits (109)	8,414.80		140 visits (140)	10,808.00
Hospital Admission	7 days (3)	13,414.10		16 days (3)	30,660.80
Hospital Visit	4 (2 adults, 2 children)	645.00		4 (3 adults, 1 child)	636.50
ER Visit	22	5,382.96		16	3,914.88
Antimicrobial	88 prescriptions (88)	1,335.83		122 prescriptions (122)	1,768.60
Absenteeism	93 days (85)	17,402.16		120 days (114)	22,454.40
Total Cost		**107,600.28**			**70,246.18**

The TSB estimated the average cost and effect per individual in both arms (see *Table 5*). The average cost per patient in the treatment arm was estimated to be $69.08 and $32.66 in the control arm. The average number of cases of influenza was estimated to be 0.04 in the treatment arm, and 0.27 in the control arm. Effect was converted to number of influenza-free cases by subtracting the average case from 1. This produced an average number of influenza-free cases of 0.96 in the treatment arm and 0.73 in the control arm. Effect was converted because the trial captured cases of influenza but a vaccination strategy's output is protection against infection, measured in this instance as influenza-free cases.

Table 5: TSB Results, Average Cost and Effect per Individual for Each Arm

TREATMENT	**CONTROL**	**DIFFERENCE**
Cost Average	*Cost Average*	
69.075	**32.662**	**36.413**
Effect Average, Cases	*Effect Average, Cases*	
0.044	**0.267**	**-0.223**
Convert Effect to Influenza –free Cases (1-effect)	*Convert Effect to Influenza –free Cases (1-effect)*	
0.956	**0.733**	**0.223**

Average costs and effects for treatment compared to control were plotted on the CEP (see *Figure 4*). As the treatment was more effective and more costly than the control an ICER was calculated, resulting in an ICER of $114.24 per case of influenza averted (Δcost/Δeffect=36.41316473/0.22280944=$164.19, rounded). 95% CI around the ICER was estimated from TSB results, resulting in a CI of $28.38, $2767.75. The values included in the CI were plotted on the CEP (see *Figure 5*) to illustrate the variance in the estimates and demonstrate the un-interpretability of CI results when negative values are included.

Figure 4: Average Costs and Effects on Cost Effectiveness Plane, Base Case

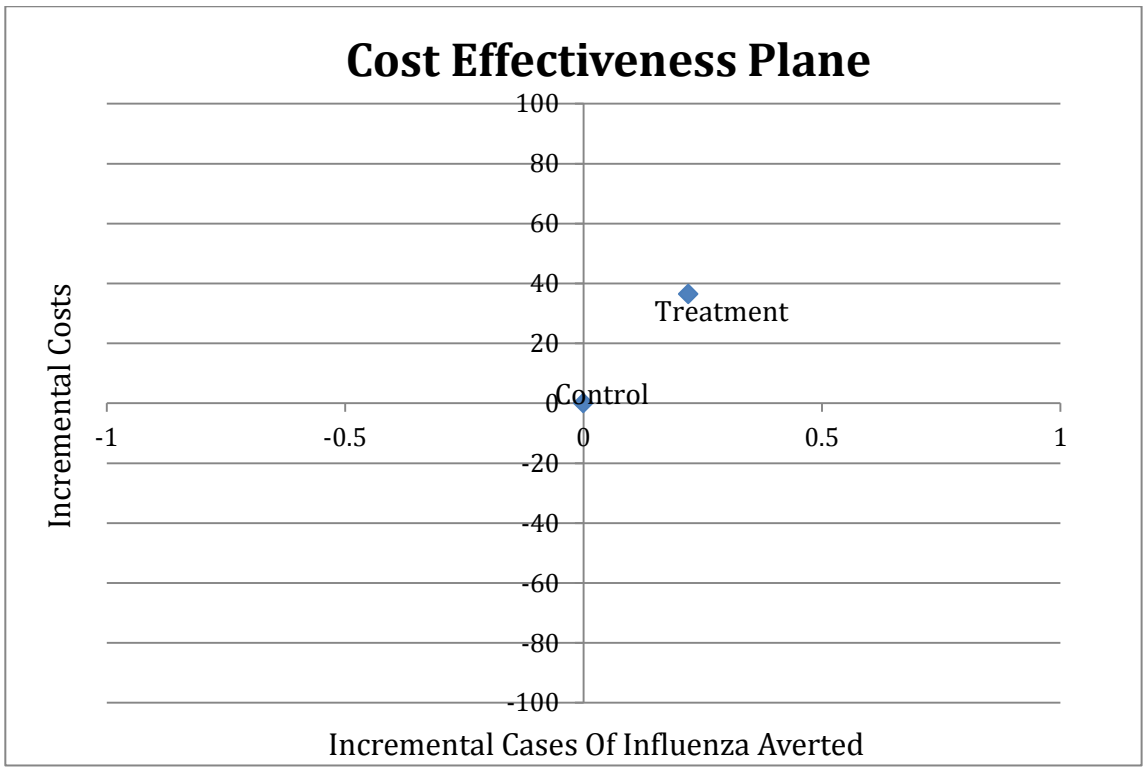
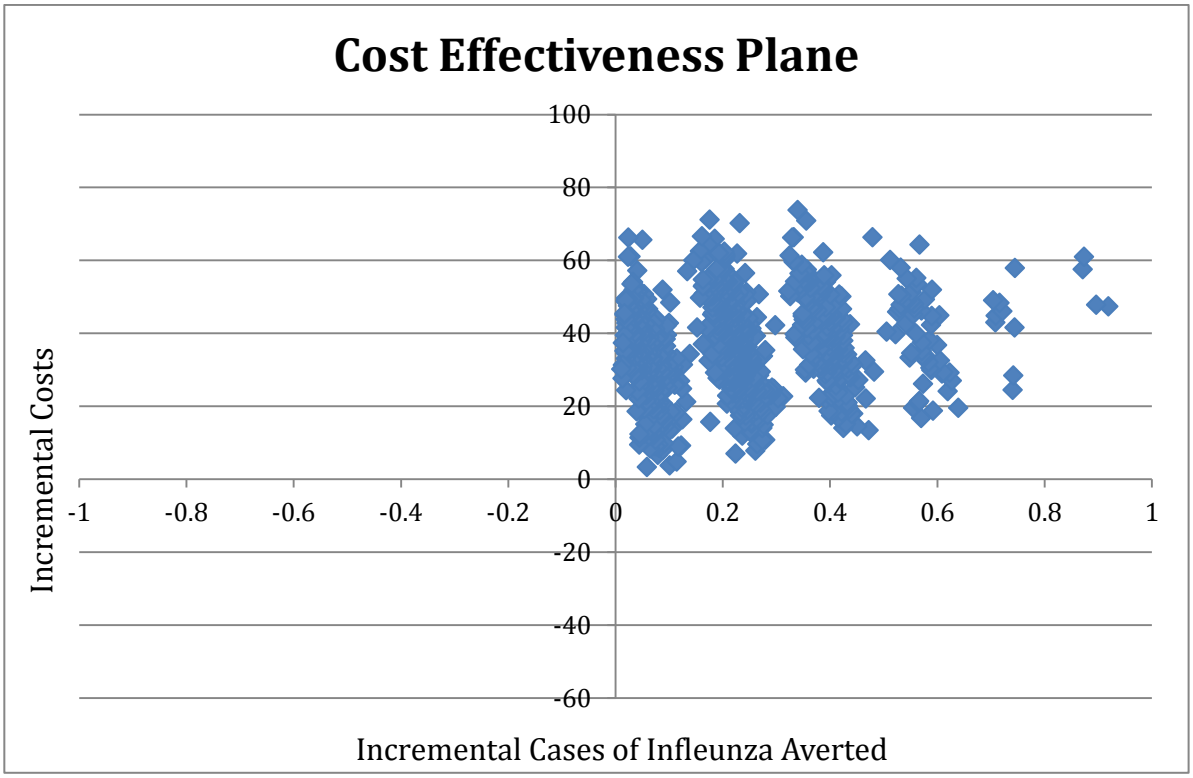


Figure 5: 95% CI of ICER on Cost Effectiveness Plane, Base Case



NMB was calculated and the average probability of each strategy being cost effective (strategy with the higher NMB value is the more cost effective choice) for a variety of WTP amounts was calculated and plotted on a CEAC to elucidate TSB results (see *Figure 6 and Table 6).* At a WTP of $177, the probability of the treatment strategy being cost effective compared to the control was 0.50.

Figure 6: Cost Effectiveness Acceptability Curve. Base Case

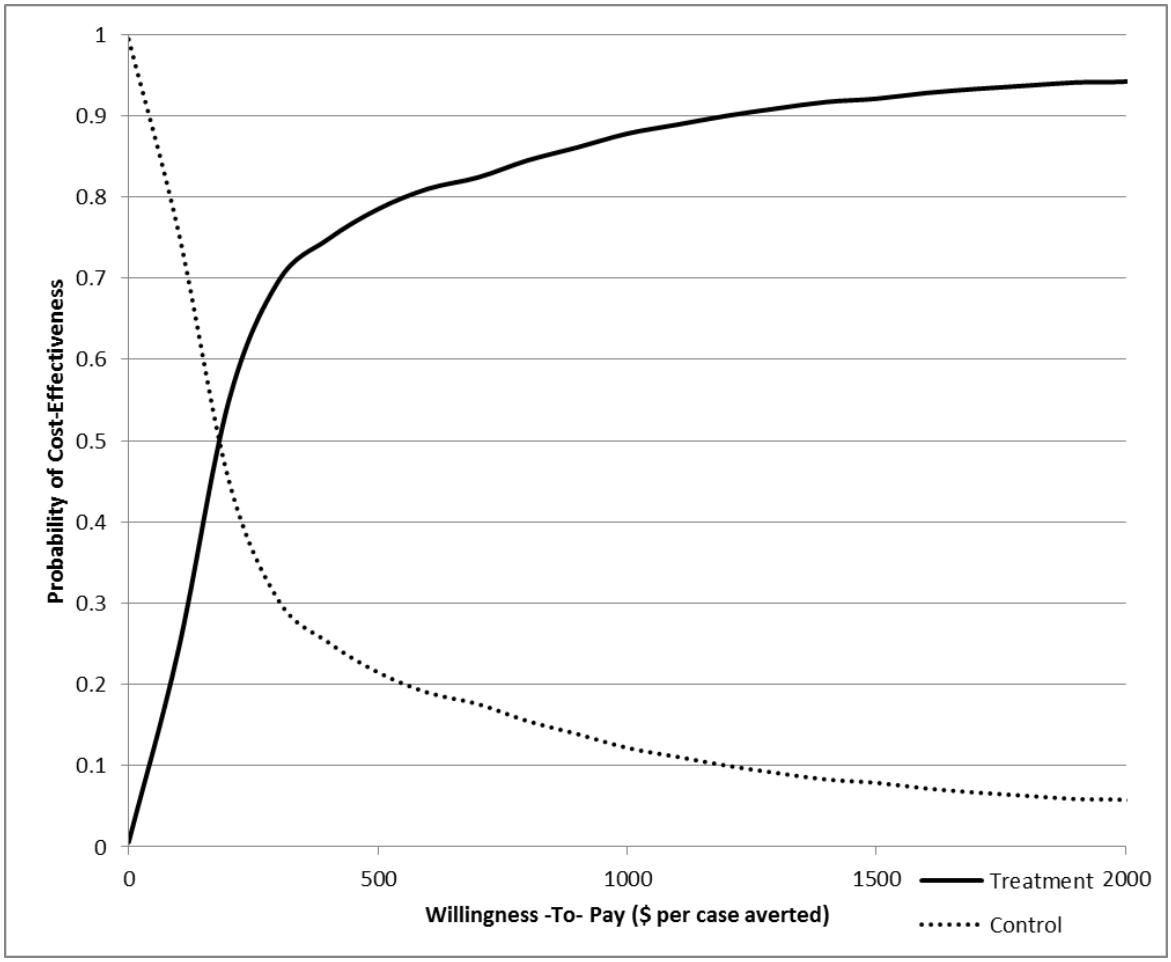


Table 6: Probabilities of Treatment being Cost Effective at Various WTP Amounts

WTP, $ per case averted	100	300	500	700	1000	2000
Probability	0.243	0.696	0.785	0.824	0.878	0.942

1. One-Way Sensitivity Analysis

Variations of five inputs, in two to three ways each, yielded 13 different TSB results, all of which showed the treatment arm to consistently be more effective and more costly than the control arm. ICERs and 95%CI surrounding ICERs were calculated for each TSB variation (see *Table 7*). NMB was also calculated for each variation analysis and converted to a cost effectiveness probability at various WTP amounts (see *Table 8).*

Table7: Mean Costs and Effects, ICERs and CIs for One-Way Sensitivity Analyses (rounded)

Variation, $	ICER, $/case influenza averted	95% CI
Base Case	164.19	28.38, 2767.75
Needle,		
.14	161.34	13.79, 2886.68
.12	129.06	-23.23, 2772.91
Nurse,		
55.20	133.57	-30.72, 2499.24
66.08	152.43	2.49, 2642.48
79.79	181.00	21.21, 3427.20
Facility,		
35.25	192.20	12.46, 2626.85
17.62	154.25	-4.933, 3208.89
5.88	130.80	-39.8011, 2229.42
Hospital Admission,		
500	173.06	45.02, 3310.07
1000	165.51	37.67, 3149.07
1500	165.78	23.74, 3011.96
Absenteeism,		
296.32	154.84	-2.59, 2682.85
124.64	172.55	34.22, 3708.24

Table 8:

Probabilities of Treatment Being Cost Effectiveness at Various WTP Amounts, One-Way Sensitivity Analysis Results

WTP, $ per case of influenza averted	**100**	**300**	**500**	**700**	**1000**	**2000**
Probabilities						
Base Case	0.243	0.696	0.785	0.824	0.878	0.942
Needle, 0.14	0.257	0.681	0.762	0.824	0.876	0.931
0.12	0.561	0.804	0.867	0.903	0.930	0.965
Nurse, 55.20	0.345	0.725	0.804	0.853	0.896	0.951
66.08	0.280	0.694	0.770	0.834	0.881	0.939
79.79	0.187	0.666	0.748	0.807	0.859	0.932
Facility, 35.25	0.180	0.633	0.723	0.795	0.861	0.929
17.62	0.280	0.691	0.775	0.830	0.875	0.940
5.88	0.355	0.713	0.801	0.849	0.901	0.949
Hospital Admission, 500	0.191	0.647	0.737	0.808	0.863	0.942
1000	0.210	0.675	0.764	0.823	0.870	0.944
1500	0.237	0.669	0.753	0.809	0.879	0.941
Absenteeism, 296.32	0.299	0.689	0.769	0.818	0.870	0.942
124.64	0.214	0.662	0.737	0.796	0.865	0.937

2. Scenario Analysis

TSB results for each scenario analysis were used to calculate mean cost and effects, ICER and 95% CI around ICER (see *Table 9*), as well as NMB and probabilities of the treatment arm being cost effective compared to the control at various WTP (see *Table 10);* CEACs were also constructed (see *Figures 7,8,9*).

Mean cost and effects for treatment arm in scenario 1, average case, were $62.45 and 0.96, and $32.00 and 0.73 in the control arm. ICER was estimated at $137.48 per case of influenza averted (95% CI, $26.26, $2347.17). Mean cost and effects for treatment arm in scenario 2, best case, were $44.06 and 0.96, and $22.02 and 0.73 in the control arm. ICER was estimated at $98.48 per case of influenza averted (95% CI, $19.16, $1753.74). Mean cost and effects for treatment arm in scenario 3, worst case, were $81.62 and 0.96, and $ 41.42 and 0.73 in the control arm. ICER was estimated at $179.60 per case of influenza averted (95% CI, $1.35, $4061.01).

Table 9: Scenario Analysis, ICER and 95% CI Results

Scenario	*ICER, $/case influenza averted*	*95% CI*
Base Case	164.12	28.38, 2767.75
1, Average Case	137.48	26.26, 2347.17
2, Best Case	98.48	19.16, 1753.74
3, Worst Case	179.60	1.35, 4061.01

Table 10: Scenario Analysis, NMB at Various WTP Results

WTP, $	100	300	500	700	1000	2000
Probabilities						
Base Case	0.243	0.696	0.785	0.824	0.878	0.942
Scenario 1, Average Case	0.316	0.728	0.816	0.869	0.914	0.959
Scenario 2, Best Case	0.457	0.768	0.854	0.896	0.926	0.966
Scenario 3, Worst Case	0.211	0.658	0.749	0.812	0.868	0.937

Figure 7: Scenario 1, Average Case, CEAC

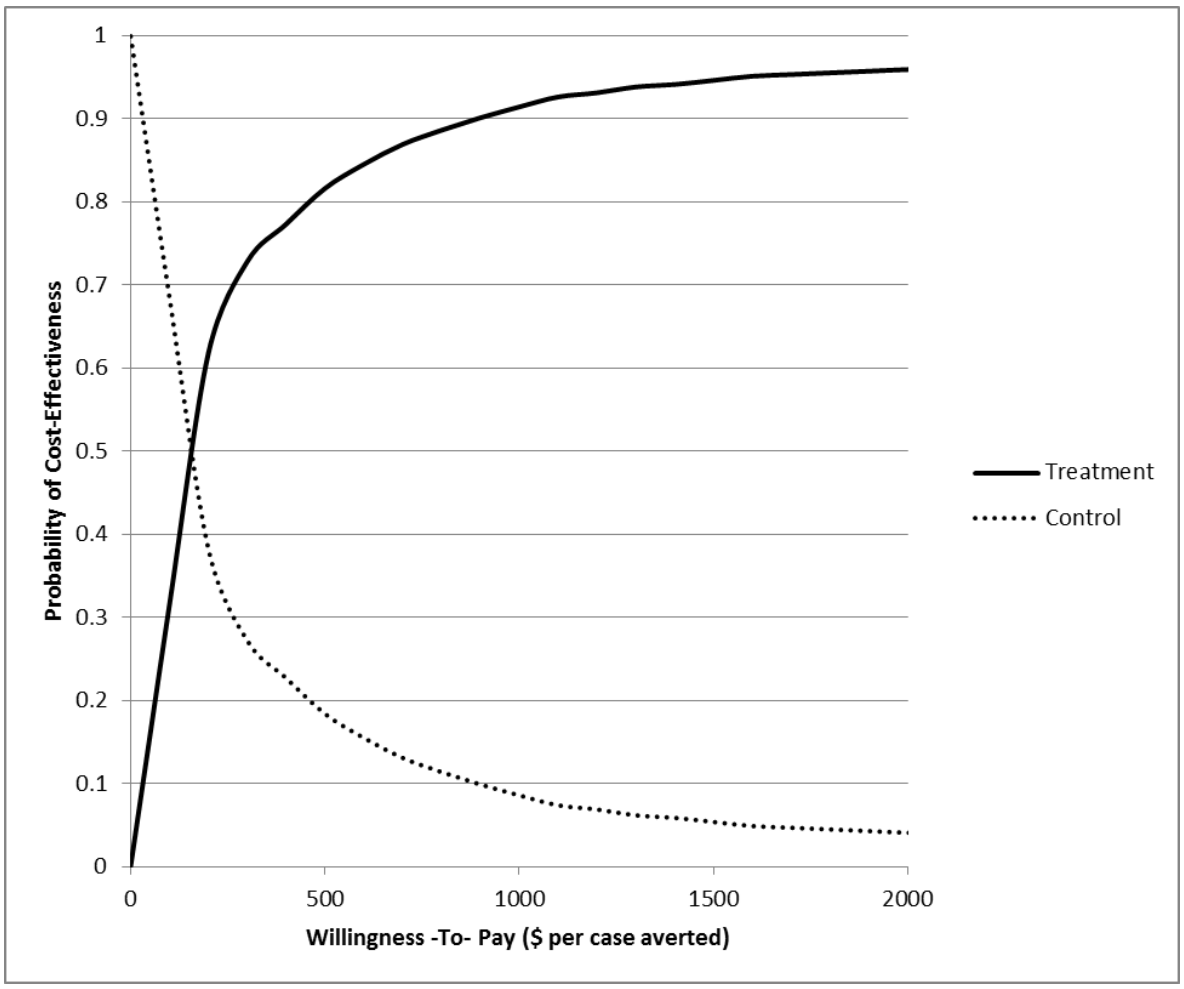


Figure 8: Scenario 2, Best Case, CEAC

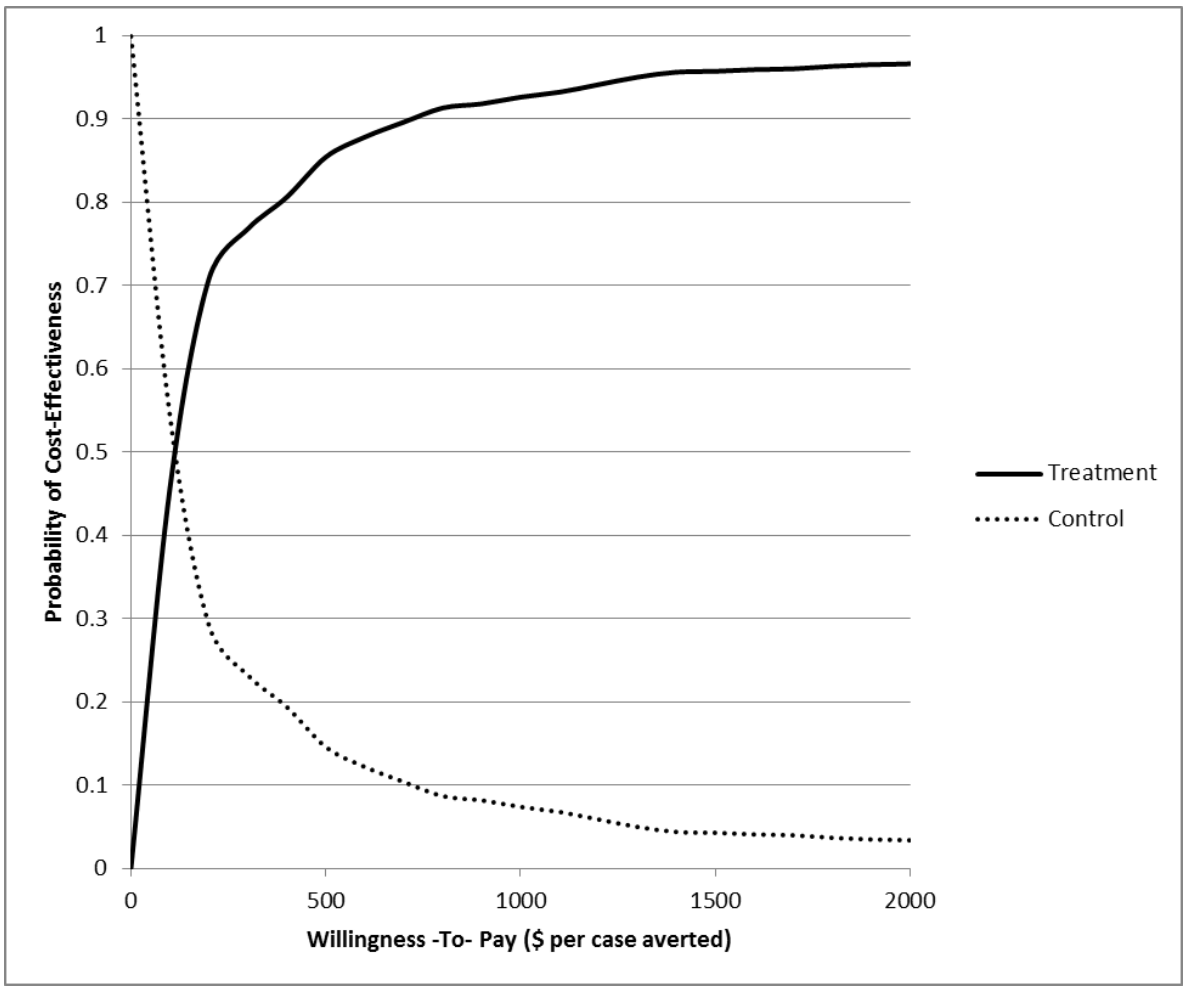
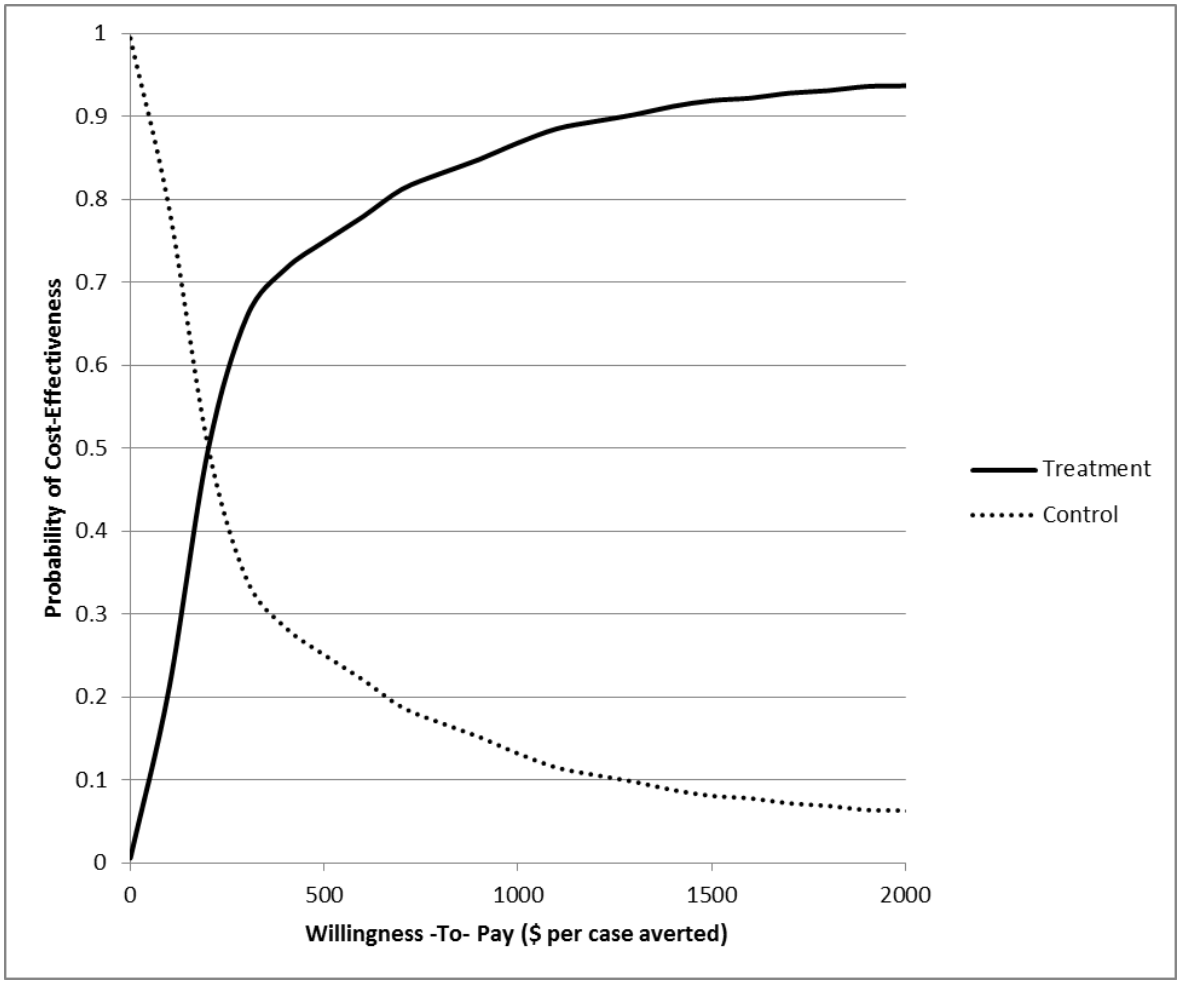


Figure 9: Scenario 3, Worst Case, CEAC



CHAPTER 4 DISCUSSION

This CEA estimated an ICER of $164.19 per case of influenza averted (CI$28.38, $2767.75). NMB showed at a WTP of $177, the probability of the treatment being more cost-effective than the control was 50%. One-way sensitivity analysis altered 5 inputs with two or three variations each for a total of 13 separate analyses. These analyses provided a range of ICER estimates from $129.06 to $192.20. NMB was calculated and CEACs were produced for each simulation. Results of these analyses proved to be very similar to base case results indicating that the base case results are robust. Scenario analysis altered multiple inputs at a time to produce an average case, best case and worst case scenario. Even with altering multiple inputs at the same time, results changed only slightly in comparison to base case results, further supporting that base case results are robust.

The largest contributor to costs was the cost of vaccination in the treatment arm, estimated to be $78,404.59. The cost of vaccination included the cost of the vaccine and needle, nursing costs and facility cost. Out of these, nursing costs accounted for the majority of vaccination costs, estimated at $55,060.50. As confirmed by sensitivity analysis, if nursing costs were reduced, for example by employing nurses at a lower position on the pay scale (starting wage for 2 nurses $55.20 per dose), costs of vaccination would be greatly reduced ($43,111.20) and ICER would be reduced to $133.57 (CI: $-30.72, $2499.24).

Both direct and indirect costs were included in this CEA, including those related to healthcare resources consumed and productivity losses due to absenteeism. When resource utilization was gathered, no healthcare related utilization (dr. visits, hospital admission, hospital visits, ER visits and antimicrobial prescriptions) were recorded as being due to influenza infection. It is possible that cases of absenteeism could have been due to influenza, though absenteeism was not recorded in such a way that specified this. To determine what the effect of including only costs due to influenza infection might have had on the CEA results a TSB was generated including costs of vaccination and estimated absenteeism due to influenza. Absenteeism was estimated by cross-referencing subjects with confirmed cases of influenza against those who had recorded absenteeism for any reason. The results of this are as follows. Average cost of treatment arm was $60.62 and average effect was 0.96. Average cost of control arm was $23.17 and average effect was 0.73. Difference in cost was $37.45 and effect was 0.51 for an ICER of $167.76 (95% CI, $19.22, $3000.19). NMB and CEAC showed at $182 the probability of the treatment arm being cost effective was 50% and at $700 it reached 81%.

1. Generalizability and Recommendations

Clinical evidence strongly suggests that directing immunization efforts at school-aged children provides a significant protective effect to all members of a community (vaccinated and unvaccinated)(7). This is of particular importance as this protective effect includes the elderly who usually suffer disproportionately in terms of bearing the majority of severe outcomes related to influenza infection in a population. Establishing a method such as the immunization of children to stimulate herd effect is very important as it provides a way to protect the elderly for whom the benefits of direct immunization are not substantiated (8). As this economic evaluation shows that the strategy of immunizing children is more effective yet more costly than not implementing the strategy, a decision needs to be made as to whether the estimated ICER of $114 for each additional case of influenza averted is good value for money. Sensitivity analysis has shown this estimate to be robust, but issues around generalizability of the CEA should also be considered before recommendations are made.

1.1. Sample Similar to Target Population

The Hutterite people studied in the trial used to inform the effect input of this CEA are similar to other Canadians in a number of ways that would allow for generalizability. In particular, families live in single-family dwellings, children go to school, men work outside the home, families shop in nearby towns, and families

have regular contact with other community members. Due to these factors influenza would spread in these communities much like it would in other Canadian communities(30).

Hutterites differ from the target population in that they are on average much healthier. They are therefore more comparable to Ontario rural populations who are typically healthier than urban populations. An ICER of $164 can be considered a conservative estimate because in a less healthy population unvaccinated communities one would expect to see higher rates of influenza infections, worse outcomes and higher costs.

1.2. Uptake of Immunization Strategy and Impact of Circulating Strains

Trial results rely heavily on the fact that uptake of children being vaccinated was 38%-100%, mean 75%, median 77%(26). This could potentially be unrealistic to achieve in a real-world setting, however if school flu clinics were initiated it could produce high-uptake in school aged children. Assuming that uptake would be similar, the results of this CEA can be generalized to Ontario, however with the changing nature of influenza this should be done cautiously. Cost and effect inputs and subsequent ICER and NMB/CEAC results are particular to this trial, Ontario, and the influenza strains circulating in 2008-2009. Cost and effects would change with a change in the virulence of the circulating strains and the susceptibility of the population each influenza season. 2008-2009

was a mild influenza season, and more sever strains would likely produce a lower ICER if not cause the treatment arm to dominate the control (treatment less costly and more effective than control). This is because more severe strains would produce more utilization of health care resources and the increased cost in the control arm would quickly out-weigh the costs in the treatment arm assuming proportionately the distribution of influenza infection was similar. Even though virulence of strains and susceptibility of populations is unpredictable $164 ICER per case averted is a conservative estimate due to a mild influenza season, and it is realistic to believe that the ICER would be lower and quite possibly the treatment strategy may dominate the control as a severe season would produce higher rates of infection, worse outcomes, and higher costs in the arm with the greater proportion of cases (control).

1.3. Generalizability of Setting

In many jurisdictions where there are not enough resources for universal vaccination and therefore a choice needs to be made as to what strategy best protects the population. If using this CEA to assist in decision making, costing would have to be adjusted to the context being considered. If the context is similar in terms of costing, or costing is found to be higher in follow-up items (doctor's visits, hospital admission et cetera) it is likely that the strategy of vaccinating children is good place to direct resources as it provides direct

protection to the children vaccinated and indirect protection to all others, including the elderly.

1.4. Recommendation

In light of the above it is recommended that the strategy of vaccinating children is good value for money, particularly because it not only protects those vaccinated but all persons in a community. In Ontario there are resources available to provide all residents with immunization against influenza, and as it is estimated that only 42% of the population gets immunized (12 years and older in 2005 survey (31)). Given this it is reasonable to assume that unused resources could be made available and be shifted to promote this strategy on top of existing strategies.

2. Usefulness of Comparing to No Strategy

The value of this economic evaluation is that is provides a good comparison of the strategy of immunizing healthy children against not implementing this strategy. In terms of aiding in decision making, this evaluation has significant value if one is considering adding this strategy to their current strategy. Decision makers can simply use the cost-effectiveness results of this CEA to determine the added value of this strategy to any current strategy.

The Hutterite Influenza Prevention Study was implemented in a milieu where only a basic influenza immunization strategy existed (current provincial strategies for Alberta, Saskatchewan, and Manitoba). There were persons who were not included in the healthy children vaccination group who were immunized outside of the study (172 in the treatment arm, 9.7% and 122 in the control arm, 11.6%). These others were not costed in the base case CEA and sensitivity analyses as the numbers were similar in each arm and therefore were unlikely to produce a noteworthy difference in outcomes. To confirm this assumption a TSB was constructed where vaccinated adults and children outside the 'healthy children group' in both the treatment and control group were assigned a vaccination cost. Adults were assigned a cost of $109.16 per dose ($17.54 for 1ml adult dose, $0.09 needle cost, $70.50 nurse cost, and $21.03 facility cost). Children >9 years old to 15 years old were assigned a cost of $100.39 ($8.77 for 0.05ml child dose, $0.09 needle cost, $70.50 nurse cost, and $21.03 facility cost). Children ≤9 were assumed to have never been vaccinated before, data was not collected to determine this. The cost assigned for vaccinating these children was $200.78, for two doses, four weeks apart. Results were an ICER of $185.15 per case of influenza averted and a CI of $-6.01, $3006.11. These results, as expected, were very similar to base case results (ICER $164.19, CI: $28.38, $2767.75), and support the exclusion of the costs of the other community members vaccinated.

3. Ethics

3.1. Implementation of the Strategy

This CEA is concerned with a strategy, that if implemented would produce a change in who the subject of promotional efforts are (to include children) and who these campaigns are geared towards (children, schools, parents). It is unlikely that this change would have moral and ethical implications related to the vaccine and strategy of immunizing for influenza as both of these are accepted in Ontario society. There are some issues around the drug itself (trivalent inactive), as it appears that using a live strain provides better protection (55) though it is more costly(56). Also some people have adverse events due to the ingredients in influenza vaccine (e.g. egg products, (57), but this is mitigated by not administering to those with known allergies and other conditions that may produce adverse reactions, and by having enough trained staff on hand to assist if an adverse event does occur.

Issues surrounding autonomy with the adoption of this strategy are minimal in Ontario. Autonomy would not be infringed upon by the adoption of this strategy as it is not mandatory for anyone to be immunized in the province (though certain workplaces require it), thereby allowing people to choose whether or not they want to be immunized. In the case of children, their parents would likely decide if they should be immunized, which would infringe on the child's autonomy to choose if parents did not honour their child's wishes. Issues of

equity with adoption are void as every Ontario resident has access to immunization with no up-front cost, due to universal vaccination. Additionally, vaccinating children would benefit all society, as demonstrated in Loeb et al 2010, as children are major proliferators of influenza (11)(19).

Aside from issues of autonomy that may arise for children, concern for their welfare should also be considered with their central role in this strategy. Fortunately it has been demonstrated that immunizing for influenza is a beneficial strategy proven to reduce the incidence of influenza in children who are vaccinated(8). This strategy can potentially cause harm to those inoculated (from reactions to the vaccine), and other adverse events are rare and minimal, usually slight pain at the injection site (26) .

4. Strengths and Weaknesses of this CEA

The strengths of this study are in large part due to the high quality of the Hutterite Influenza Prevention Study. Strengths of the Hutterite Influenza Prevention Study include follow up of community members in addition to children vaccinated, measurement of influenza cases in all participants with laboratory confirmed testing, inclusion of a wide age range of children (36 months to 15 years), and the cluster design of the trial which allowed for a unique opportunity to observe the effects of influenza vaccination within the communities. Another strength of this CEA is that this study uses TSB, which takes into account both

clustering and the correlation of cost and effect, and the application of a shrinkage correction for unequal clusters. TSB is one of the methods recommended for estimating cost-effectiveness from CRTs (2). Another strength is that this study calculated ICER and NMB/CEAC to estimate cost-effectiveness, which allows the reader to have a clearer picture of the probability of a strategy being cost-effective particularly when CI of the ICER possess negative values.

Weaknesses of this study are that some cost inputs may have been overestimated, such as facility rental and cost of hospital admission. However, these inputs were tested in sensitivity analysis and showed to be of little influence on results. Also doctor's visits for influence were likely underestimated as participants may have decided not to see a doctor for influenza type illness as they were seeing a nurse two times a week. This possible underestimation could be dismissed, as the outcome would be equal in each arm of the trial due to large sample size and randomization of communities.

5. Other Economic Evaluations on the Strategy

There were no other economic evaluations that could be found that estimated the cost-effectiveness of an influenza vaccination strategy (using inactive vaccine) directed at immunizing healthy children and measuring the resulting incidence of influenza in the entire community, and measuring incidence with laboratory confirmed cases of influenza, against any comparator. Similar

economic evaluations do not consider effect of persons beyond those who have been immunized (56,58), which without this consideration the full benefit of a population public health initiative such as influenza vaccination goes un-captured. Another similar evaluation examined the effect of immunizing children on families and reported a net cost of vaccination and net cost per case of influenza due to average individual estimated showing a lower cost and greater effect (59). Effect in this trial was cases of influenza collected by patient reporting. This is not an accurate measure of the incidence of influenza for a number of reasons. For instance, influenza is indistinguishable from other respiratory illnesses, some cases of influenza are asymptomatic, and recall bias from patient reporting. Inaccurate effect measurement will lead to inaccurate cost-effectiveness results. Additionally, including vaccinated children aged 2-5 years only captures a small portion of the strategy's capability to induce herd effect.

6. Conclusion

This CEA can be used in contribution to decision making of whether or not to adopt an influenza immunization strategy directed at children. Because of the variability in costs across jurisdictions and countries, as well as the variation of the impact of future influenza strains, the results of this CEA should be used cautiously. The results of this CEA are simply estimates of cost-effectiveness, particular to a specific and mild influenza season (2008-2009), in a healthy study

population in an Ontario context. A more virulent season and a less healthy population would have produced a lower ICER or seen the treatment arm dominate the control.

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APPENDIX 1: Cluster Sizes Per Arm

Treatment Arm, Clusters=22, Subjects=1773		Control Arm, Clusters=24, Subjects=1500	
Cluster Number	Number of Subjects in Cluster	Cluster Number	Number of Subjects in Cluster
1	28	1	47
2	45	2	65
3	75	3	45
4	91	4	54
5	76	5	57
6	74	6	23
7	94	7	109
8	98	8	31
9	96	9	45
10	102	10	19
11	97	11	71
12	51	12	58
13	96	13	46
14	114	14	68
15	85	15	55
16	78	16	69
17	105	17	70
18	45	18	74
19	76	19	123
20	74	20	69
21	80	21	70
22	92	22	50
		23	116
		24	66

APPENDIX 2: Baseline Characteristics of Study Participants
Adapted from Loeb et al. 2010 (7)

Variable	Treatment 22 Clusters n=1773	Control 24 Clusters n=1500
Age, mean (SD) years	25.9 (19.9)	26.0 (20.0)
Age groups, years, number, (%)		
<3	96 (5.4)	86 (5.7)
3-15	633 (35.7)	553 (36.9)
16-49	793 (44.7)	650 (43.3)
50-64	166 (9.4)	136 (9.1)
>64	85 (4.8)	75 (5.0)
Female sex, number (%)	1010 (60.0)	848 (56.6)
Vaccinated against influenza, number (%)	172 (9.7)	122 (11.6)
≥1 Coexisting Condition, number, (%)	170 (9.6)	133 (7.2)
Asthma	69 (3.9)	45 (3.0)
Congestive heart failure	8 (0.5)	4 (0.3)
Blood disorders	15 (0.8)	11 (0.7)
Compromised management of respiratory secretions	8 (0.4)	6 (0.4)
Diabetes	42 (2.4)	40 (2.7)
Immuncompromised	12 (0.7)	13 (0.9)
Other **	3 (0.2)	3 (0.2)
Clusters, mean (SD), number		
All residents per colony	89.7 (22.7)	76.6 (24.6)
Enrolled participants per colony	80.6 (21.7)	62.5 (25.6)
Households per colony	22.2 (8.4)	18.3 (7.0)
Age 3-15 years, given study vaccine	22.8 (7.6)	18.5 (8.7)

* Percentages may not sum to 100 due to rounding
** One participant with liver disease, one with kidney disease, and one with chronic obstructive lung disease in each arm

APPENDIX 3: Formula For Two-Stage Bootstrap with Shrinkage Correction

From Gomes et al. 2011 (2)

Appendix 2 – Algorithms for the non-parametric two-stage bootstrap

Suppose we have M_k clusters randomized to treatment (k=2) and control (k=1), with n_j individuals within each cluster j.

Algorithm 2 – Routine with the shrinkage correction

1. For i in 1 to n_j individuals in cluster j.
2. For j in 1 to M_k clusters in treatment k.
3. For k in 1 to 2 treatments.
4. Calculate shrunken cluster means, $\hat{x}_j^c$ and $\hat{x}_j^e$, for cost and effect[1].
5. Calculate standardized individual-level residuals, $\hat{z}_{cost,ji}$ and $\hat{z}_{effect,ji}$, for cost and effect[2].
6. Randomly sample (with replacement) M_k pairs of cluster means, $x^*_{cost,j'}$ and $x^*_{effect,j'}$, from the shrunken cluster means calculated in step 4.
7. Randomly sample (with replacement) $\sum_{j'=1}^{M_k} n_{j'}$ pairs of residuals, $z^*_{cost,i'}$ and $z^*_{effect,i'}$, where i'=1... $\sum_{j'=1}^{M_k} n_{j'}$, from the standardized residuals calculated in step 5. Note that the hierarchical structure is ignored in this step.
8. Re-construct the sample ($y^*_{cost,j'i'}$, $y^*_{effect,j'i'}$) by adding the shrunken cluster means from step 6 and the standardized residuals from step 7, i.e. $y^*_{cost,j'i'} = x^*_{cost,j'} + z^*_{cost,i'}$ where $i' = 1 \ldots n_{j'}$ and likewise for effects; call it a "synthetic" sample.

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[1] $\hat{x}_j^c = c\bar{y}_{..}^c + (1-c)\bar{y}_j^c$ where c is given by $(1-c)^2 = \frac{M_k}{M_k - 1} - \frac{SS_W}{b(b-1)SS_B}$; SS_w= within-sum of squares and SS_B = between-sums of squares, b = average cluster size (a formulation akin to the harmonic mean is used here; see page 412 in Smeeth and Ng (31). These are similarly calculated for effect and separately so for the two strata (treatments). Note that j' is the new cluster identifier (=1 to M_k) which may contain repeats of the old cluster identifier, j. All these calculations take place before sampling.

[2] $\hat{z}_{cost,ji} = \frac{y_{cost,ji} - \bar{y}_{cost,j.}}{\sqrt{1-b^{-1}}}$, where $y_{cost,ji}$ is the observed cost for the i-th individual in cluster j. These are similarly calculated for effect and separately for the two strata (treatments). Again, all these calculations take place before sampling.

9. Repeat steps 4 to 8 for each stratum (treatment) and stack these 'synthetic' samples into a single bootstrap sample.
10. Compute the parameter of interest, INB, by INB = Δeffect × λ - Δcost where Δcost = $\bar{y}^*_{cost,treatment} - \bar{y}^*_{cost,control}$ and likewise for Δeffect.
11. Replicate steps 6 to 10 *R* times to form a bootstrap distribution of INB, i.e. a distribution constructed by *R* replicates of INB.
12. Compute the bias-corrected and accelerated CIs around the mean INB.