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ECONOMIC EVALUATION OF AN INFLUENZA IMMUNIZATION STRATEGY OF HEALTHY CHILDREN

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Objectives: Vaccinating healthy children is proposed as a strategy to produce a herd effect and protect vulnerable groups. The Hutterite Influenza Prevention Study investigated this strategy, comparing communities with or without childhood influenza immunization programs. There are costs associated with vaccination therefore there may be a trade-off between these costs and the benefits of avoiding influenza cases. This evaluation estimates the cost-effectiveness of immunizing only healthy children in preventing cases of influenza within entire communities.

Methods: Effect data and resource utilization were collected during the trial. Cost data were collected from payer, literature and Internet sources. A two-stage bootstrap (TSB) with shrinkage correction was used to estimate average costs and effects. The incremental cost effectiveness ratio (ICER) and sample uncertainty around this estimate were calculated from the TSB results.

Results: Mean costs per patient for the treatment and control arms were $69.07 and $32.66 (difference $36.41). Mean number of influenza cases for the treatment and control arms were 0.04 and 0.27 (difference 0.23). ICER was $164.12 ($28.38, $2767.75) per case of influenza averted.

Conclusions: Immunizing healthy children for influenza is more costly, yet more effective than no immunization in preventing cases in the sample. At a cost of $164.12 to prevent a case of influenza, immunizing healthy children to protect all community members may be considered costeffective. Estimated results are conservative as the influenza season was mild and the sample population was healthy. In a more severe season with a less healthy population the ICER is expected to decrease.

Keywords: Human Influenza, Influenza Vaccines, Medical Economics, Child, Adolescent

Influenza can cause substantial morbidity and mortality in a population, which varies regularly due to changes in circulating viruses and the susceptibly of a population (1). It is difficult to estimate the incidence of influenza due to several factors. For example influenza is clinically indistinguishable from other viral respiratory infections (2) and not everyone seeks a healthcare professional when infected.

Vulnerable groups such as the elderly suffer disproportionately from seasonal influenza in terms of severe outcomes such as hospitalization and mortality (3). Vaccination strategies aim to protect a population from infection; however, evidence does not support that benefit is produced from direct vaccination of this vulnerable group (2).

It has been proposed that vaccinating only healthy school-aged children could create a herd effect that protects entire communities, although evidence is limited (4). Herd effect is defined as "the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population" (5). This strategy is suggested as children are major propagators of influenza (6;7) and they respond favorably to direct vaccination (2). Previous trials exploring the validity of this strategy have produced varying, although predominantly supportive results (8–14). This is likely due to different measures of effect, such as hospitalizations or deaths due to influenza, or patient reported illness. In a recent study, the Hutterite Influenza Prevention Study (14), effect was measured with laboratory confirmation of the virus. This trial supported the strategy of immunizing healthy children to protect entire communities.

To our knowledge a cost-effectiveness analysis on this strategy of vaccinating healthy children that measures effect as cases of influenza confirmed with laboratory tests in entire communities does not exist. As recent evidence demonstrates this strategy to be effective in protecting the children vaccinated as well as unvaccinated community members (14), the results of an economic evaluation would be useful to decision makers to assist in choosing a cost-effective strategy in a resource-scarce environment. We, therefore, conducted an economic evaluation, cost-effectiveness analysis (CEA), of the Hutterite Influenza Prevention Study (14). Data were collected on resource use alongside the trial to estimate the cost-effectiveness of vaccinating healthy school-aged children for influenza.

METHODS

Overview

The Hutterite Influenza Prevention Study was a 3-year multicenter, blinded, cluster randomized controlled trial (CRT)

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	$70.50	Singh, Hutterite Influenza Prevention Study-data on file
Facility	$21.03	St Paul Church, Innisfil Ontario
Total vaccination cost	$100.39/dose	
Follow-up costs		
Dr. Visit	$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 Adult (>15) 500/day Children (≤15) 250/day	$19.21$9.63	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
Value of lost work/school day	$187.12	Statistics Canada, Average Hourly Wage x 8

conducted in three Canadian provinces, Alberta, Saskatchewan and Manitoba. The Hutterite people are a communal branch of Anabaptists that live in rural areas. The study included forty-six rural communities (22 treatment 24 control) and 3,273 participants, following 947 vaccinated children (502 treatment, 445 control) and 2,326 unvaccinated community members (1,271 treatment, 1,055 control). Included communities were small in size and the majority of community members were included in the study. Entire communities were randomized to either inactivated trivalent influenza vaccine or hepatitis A vaccine. Hepatitis A vaccine was chosen as the control to provide benefit to participants in the control arm. 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 6 months, the duration of the influenza season.

Clinical results of the study showed influenza cases to be 80 of 1,773 (4.5%) in the treatment arm, and 159 of 1,500 (10.6%) in the control arm. This resulted in a relative protective effect of 59% (5–82%; $p = .04$). In the unvaccinated influenza cases were 39 of 1271 (3.1%) in the treatment arm, and 80 of 1055 (7.6%) in the control arm. This resulted in an indirect protective effect of 61% (8–83%; $p = .03$). Influenza infections were distributed across age groups as follows: there were 38 cases in participants aged 0 to 4 years; 65 in those aged 5 to 10 years, 57 in those aged 11 to 15 years, and 79 in those aged 16 years and older. Full details of the study design and clinical findings of the Hutterite Influenza Prevention Study have been described elsewhere (14).

This CEA estimated the costs, effects and cost-effectiveness of the vaccination strategy in the treatment arm and the control arm of the trial. Costs were estimated using healthcare resource use data that were collected for each participant as part of the trial. Costs are in Canadian Dollars. The effectiveness measure used in the analysis was the proportion of community members acquiring influenza. The time horizon of the analysis was 6 months using data from the first year of the trial (2008–2009). Discounting of costs and outcomes was not necessary as effect of influenza vaccination is only for the duration of one influenza season, and no long-term outcomes were present in this year of the trial. The CEA took a societal perspective. After costs and effects are estimated, it will be determined whether one strategy dominates (less costly, more effective) the other strategy. If neither strategy is found to be dominant, the incremental cost-effectiveness ratio (ICER) will be calculated as the incremental cost per influenza case averted. Uncertainty in cost-effectiveness was evaluated using bootstrap techniques and expressed using a cost-effectiveness acceptability curve (CEAC). The CEAC will present the probability that the vaccination program is cost-effective at different willingness to pay (WTP) thresholds. See Supplementary Figure 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000397.

Resource Use and Costs

Resource use was collected at the level of individual subjects during the trial (Supplementary Figure 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000397.).

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Methods used to collect data were a self-reporting checklist per household confirmed by study nurses. Twice weekly nurses assessed all study participants for signs and symptoms of influenza and recorded all-cause healthcare resource usage and absenteeism from school or work. Healthcare resource usage included doctor visits, hospital visits and admissions, emergency room (ER) visits, and antimicrobial prescriptions.

Unit costs were applied to healthcare resources consumed by each subject during vaccination and follow-up. Table 1 presents the various resources included in the analysis and their unit costs. Protocol driven costs were excluded from the analysis. Influenza vaccination costs were calculated per dose. Follow-up costs were calculated per visit (doctor, ER, and hospital visits) with the exception of hospital admission, which was calculated per day.

Cost of the vaccine was estimated from a per dose purchase at a local pharmacy. It should be noted that costs to payers are likely lower due to purchasing vaccines in high volumes. Vaccination costs were estimated per dose and included cost of vaccine, needle (which was not included in the cost of the vaccine), wages for two nurses required to administer vaccine (one to administer, the other present in case of adverse event), and facility rental to administer vaccine. Nurse time included travel, set up, vaccination administration, and adverse event care. Facility rental time was estimated by dividing the total recorded hours of one nurse in the vaccination portion of the trial, by the number of doses administered.

Follow-up costs included doctor's visits, ER visits, hospital visits and admissions, antimicrobial prescriptions, and absenteeism from work or school. The cost of doctor visits were based on the fee for a general assessment listed in the Ontario Health Insurance Plan (OHIP) schedule of benefits 2011 (15). Costs for hospital admission were calculated from the Ontario Case Cost Initiative (OCCI) for acute inpatient influenza upper respiratory tract infection 2009–2010 (16). Hospital visits were assumed to be visits to a hospital clinic to see a respirologist. Costs were determined from the OHIP schedule of benefits for respirology disease consultation (15). ER visits were estimated by adding the average cost of ER physician consultation from the OHIP schedule of benefits (15) to the estimated nonphysician costs to the hospital (17). The cost of an antimicrobial course was estimated by taking the average number of days of antimicrobials prescribed for all participants per arm. The average was estimated to be the same for each arm (8 days). Dosing of levofloxacin was taken from Up To Date (18), a clinician resource for evidence-based medicine. Cost of work/school absenteeism was estimated by taking the average hourly wage for a Canadian from Statistics Canada (19) and multiplying it by eight for a daily estimate. Child school absenteeism was costed the same as adult absenteeism as it was assumed that if a child was sick at home an adult caregiver would need to be present to care for them.

All cost data were complete except for some cases of missing data in the number of days antimicrobials were prescribed. Missing values were inputted with the group mean for drug course (8 days). Costs were estimated from an Ontario perspective and were assessed in 2011 Canadian dollars. Where necessary, costs were adjusted to 2011 using the Bank of Canada inflation calculator (20). Costs were estimated at the level of individual subjects.

Effect, Cases of Influenza

Nurses visited each participant twice a week during the follow-up period to collect data on resource usage and incidence of influenza. If a participant reported influenza like illness a nasopharyngeal swab was taken and sent to a laboratory for confirmation. Influenza cases were laboratory confirmed by reverse transcriptase polymerase chain reaction (PCR) and recorded.

Statistical Analysis

It is advised that cost-effectiveness of CRTs be estimated using methods that consider clustering and correlation of costs and effects to ensure accuracy of point estimates and statistical uncertainty (21). Following this, costs and effects were analyzed jointly with a two stage nonparametric bootstrap (TSB) with an added shrinkage estimator algorithm to correct for overestimation of variance that may have occurred in second stage resampling or from unequal cluster size. To construct the TSB with shrinkage correction, shrunken means were calculated for each cluster within each arm, followed by calculation of residuals for each subject within each cluster. Next, for each arm the shrunken means and individual residuals were combined to produce a cost and effect pair for each participant. Then clusters were re-sampled with replacement and individual costs and effects within each cluster were re-sampled with replacement. Subsequently the grand mean of each arm was calculated, comprised of all the cluster means, and finally the entire process was repeated 1,000 times to produce an average individual cost and effect per arm. All calculations for the TSB with shrinkage correction were based on methods presented by Gomes et al. (22).

Incremental costs and incremental benefits were generated from the data produced by the TSB to estimate ICER, yielding a cost per case of influenza averted. Subsequently, net monetary benefit (NMB) was calculated and CEACs were constructed.

Sensitivity analysis was conducted to explore the uncertainty of ICER and CEAC results. Uncertainty around resource costs assumptions were explored with one-way and multi-way sensitivity analysis. All estimated resource cost parameters were varied including costs of needle, nurse, facility rental, hospital admission, and absenteeism. Sensitivity analysis on parameters were conducted using ranges of estimates collected from alternative sources by means of Internet searches (needle [23], nurse [24] and facility rental cost [25–27]) and variation of base-case estimates at source (value of absenteeism by profession, Statistics Canada [23]). Cost per day of hospital admission

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was also varied at $500, $1,000, and $1,500 per day (base case, $1,916.30).

Fixed parameters, those that were considered to be the true value of the parameters, were not included in the sensitivity analysis. These included cost of vaccine, doctor's visit, hospital visit, ER visit, and antimicrobial prescription. The parameters were informed by the OHIP schedule of benefits and fees, and the Ontario Public Drug Programs e-formulary. Influenza cases were laboratory confirmed by reverse transcriptase PCR and were, therefore, considered fixed.

Estimated parameters were varied one at a time in one-way sensitivity analysis, and simultaneously in multi-way analysis. Multi-way analysis was a scenario analysis, of worst case, average case, and best case. For worst case, the highest estimates were inputted; for average case, the average estimates were inputted; and for best case, the lowest estimates were inputted. Structural uncertainty of the cost equation was explored by considering only influenza related costs in the analysis. Following this, only cost of immunization in the treatment arm and absenteeism from influenza in each arm was included.

Absenteeism due to influenza was calculated by cross-referencing participant days of school or work absent with presence of laboratory confirmed influenza. See Table 2 and Table 3 for parameter variations in sensitivity analyses.

RESULTS

Base Case

Total number of cases of influenza in the treatment arm was 95 (5.4%) and 159 (10.6%) in the control arm. The TSB with shrinkage correction estimated the mean number of influenza cases to be 0.05 for the treatment arm and 0.28 for the control arm (difference 0.23). Total costs were $93,187.86 for the treatment arm and $69,949.94 for the control arm (all costs are estimated to the second decimal place based on best available information and do not suggest an increased level of costing precision). Vaccination costs accounted for $63,963.90 in the treatment arm. Estimated mean costs per patient for the treatment and control arms were $51.32 and $33.26, respectively (difference $18.06).

The incremental cost per influenza case averted was estimated to be $164.12, 95% confidence interval (CI) $28.38, $2767.75. As indicated by the CEAC the treatment arm becomes the more cost-effective strategy at a WTP of $178 (50.2%) and at a WTP of $1,000 the likelihood of the treatment arm being cost-effective is 87.8%.

Sensitivity Analysis

One-way sensitivity analysis on the cost-effectiveness results is shown in Table 4. These results varied only slightly from the base case, $164.12, ranging from an ICER of $130.30 (CI$-39.80, $2229.42) to $192.20 (CI$12.46, $2626.85). Multi-way scenario analysis ICER results for best case were $98.48 (CI$19.16, $1753.74), for average case $137.48 (CI$26.56, $2347.17), and for worst case $179.60 (CI$1.35, $4061.01). Multi-way sensitivity results are shown in Table 4.

When including only influenza related resource usage in the cost equation, the ICER was estimated at $167.77 per case of influenza averted (CI $19.22, $3,000.19). According to the CEAC, the treatment arm becomes the more cost-effective strategy at a WTP of $200 (57.23%). At a WTP of $1,000, the likelihood of the treatment arm being cost-effective is 86.5%.

Table 2. One-Way Sensitivity Analysis Variations

Parameter	Base-case	Variation	Source
Needle	$0.09		Vereburn Medical Supply
		$0.14	Cascade Healthcare Solutions
		$0.12	Midpoint Estimate
Nurse	$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	$21.03		St Paul Church, Innisfil Ontario
		$35.25	St. Mark's Church, NOTL
		$17.62	Canadian Legion, Stouffville
		$5.88	Canadian Legion, Acton
Hospital admission	$1,916.30		OCCI acute influenza per day
		$500	Expert Opinion[a]
		$1000	Expert Opinion[a]
		$1500	Expert Opinion[a]
Value of lost work/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

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Table 3. Multi-Way, Scenario Sensitivity Analysis Variations

Parameter	Base-case	Best-case	Average-case	Worst-case
Needle	$0.09	$0.09	$0.12	$0.14
Nurse	$70.50	$55.20	$67.89	$79.79
Facility	$21.03	$5.88	$19.95	$35.25
Hospital admission	$1,916.30	$500.00	$1229.08	$1916.30
Value of lost work/school day	$187.12	$124.64	$202.69	$296.32

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Table 4. One-Way and Multi-way Sensitivity Analysis Results

	Input	ICER $ (95% confidence interval)
Base-case		164.12 (28.38, 2767.75)
One-way sensitivity		
Needle	$0.12	158.04 (19.09, 3155.66)
	$0.14	161.36 (13.79, 2886.68)
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	$5.88	130.30 (−39.80, 2229.42)
	$17.62	154.25 (−4.95, 3208.89)
	$35.25	192.20 (12.46, 2626.85)
Hospital admission	$500	173.06 (45.02, 3310.07)
	$1000	165.51 (37.67, 3149.09)
	$1500	165.78 (23.74, 3011.96)
Absenteeism	$124.64	172.55 (34.22, 3708.24)
	$296.32	154.84 (−2.59, 2682.85)
Multi-way sensitivity		
Best-case		98.48 (19.16, 1753.74)
Average-case		137.48 (26.56, 2347.17)
Worst-case		179.60 (1.35, 4061.01)

DISCUSSION

Base Case

Cost and effect inputs and subsequent ICER/CEAC results are specific to the Hutterite Influenza Prevention Study, Ontario, and the 2008–2009 influenza strains. Parameter inputs and results would change if the virulence of the viruses changed as well as the susceptibility of the population. The Hutterites are a healthy group, as shown in baseline characteristics of the population studied: participants had few morbidities and were a young population. This coupled with a mild influenza season in 2008–2009 resulted in a higher ICER. If the strains were more virulent and the population more susceptible (less healthy, more vulnerable persons such as the elderly), one would expect to see larger costs in the control arm. This would result in a lower ICER, if not the domination of the treatment arm (less costly and more effective) over the control arm.

Sensitivity Analysis

One-way sensitivity analysis showed only a slight variation in results compared to base case. The largest variations from base case were from facility costs being reduced to $5.88 from $21.03 per dose, yielding an ICER of $130.30, and from nursing costs being reduced to $55.20 from $70.50 per dose, yielding an ICER of $133.57.

Multi-way scenario analysis showed the best-case scenario yielding an ICER of $98.48, a result expected if all cost estimates are inputted at their lowest value. Of interest, the worst-case scenario results are only slightly above the base-case estimate: $179.60 versus $164.12.

Altering the structure of the cost equation to include only costs related directly to influenza (vaccination of treatment group and absenteeism due to confirmed influenza) yielded very similar ICER results to base case: $167.76 versus $164.12.

LIMITATIONS

Some cost inputs may have been overestimated (e.g., facility rental and hospital admission); however, these inputs were tested in sensitivity analysis and showed to have a very small impact on the results. The cost of the vaccine was likely overestimated due to costing on a per dose basis in a pharmacy and not high volume purchasing. Additionally, the frequency of doctor's visits was likely underestimated as each participant saw a study nurse two times a week. It would have been difficult to predict what the cost and frequency of these two parameters would be in a real world setting. The probable inaccuracy of both of these parameters favors the control arm and, therefore, users of this evaluation can be confident that the estimated results of this analysis are conservative.

RECOMMENDATION

It has been demonstrated with strong evidence that this strategy created a herd effect: vaccinating only healthy children is effective in protecting the unvaccinated segment of a population (14). Additionally, a recent systematic review shows that evidence is inconclusive that direct vaccination of the elderly provides protection against influenza (2), making this strategy worth consideration. The ICER at $164.12 per case averted has been shown to be reduced if costs of nursing and facility rental costs are lowered, and these combined with high volume purchasing of a vaccine would likely result in a lower ICER. It is reasonable to assume in a more susceptible population and with more virulent influenza strains that the treatment arm would dominate the control, and the strategy would be cost saving. It is, therefore, recommended that this strategy be adopted.

SUPPLEMENTARY INFORMATION

Supplementary Figure 1:
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CONFLICTS OF INTEREST

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