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ORIGINAL RESEARCH

Cost-effectiveness analysis of intranasal live attenuated vaccine (LAIV) versus injectable inactivated influenza vaccine (TIV) for Canadian children and adolescents

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Jean-Eric Tarride[1,2]
Natasha Burke[1,2]
Camilla Von Keyserlingk[1,2]
Daria O'Reilly[1,2]
Feng Xie[1,2]
Ron Goeree[1,2]

[1]Programs for Assessment of Technology in Health (PATH) Research Institute, St Joseph's Healthcare Hamilton, Hamilton, [2]Department of Clinical Epidemiology and Biostatistics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Background: Influenza affects all age groups and is common in children. Between 15% and 42% of preschool- and school-aged children experience influenza each season. Recently, intranasal live attenuated influenza vaccine, trivalent (LAIV) has been approved in Canada.

Objective: The objective of this study was to determine the cost-effectiveness of LAIV compared with that of the injectable inactivated influenza vaccine, trivalent (TIV) in Canadian children and adolescents from both a payer (eg. Ministry of Health) perspective and a societal perspective.

Methods: A cost-effectiveness model comparing LAIV and TIV in children aged 24–59 months old was supplemented by primary (ie, a survey of 144 Canadian physicians) and secondary (eg, literature) data to model children aged 2–17 years old. Parameter uncertainty was addressed through univariate and probability analyses.

Results: Although LAIV increased vaccination costs when compared to TIV, LAIV reduced the number of influenza cases and lowered the number of hospitalizations, emergency room visits, outpatient visits, and parents' days lost from work. The estimated offsets in direct and societal costs saved were CAD$4.20 and CAD$35.34, respectively, per vaccinated child aged 2–17 years old. When costs and outcomes were considered, LAIV when compared to TIV, was the dominant strategy. At a willingness to pay of CAD$50,000 per quality adjusted life year gained, or CAD$100,000 per quality adjusted life year gained, the probabilistic results indicated that the probability of LAIV being cost-effective was almost 1.

Conclusions: LAIV reduces the burden of influenza in children and adolescents. Consistent with previously reported results, vaccinating children with LAIV, rather than TIV, is the dominant strategy from both a societal perspective and a Ministry of Health perspective.

Keywords: influenza, vaccine, children, cost-effectiveness

Introduction

Due to its high prevalence and associated morbidity and mortality, influenza is a major public health concern that affects millions of Canadians every year. It is estimated that every year between 2000 and 8000 Canadians die of influenza or its complications, depending on the seasonal severity.[1] Although influenza affects all age groups, influenza infection is most common in children, as between 15% and 42% of preschool- and school-aged children each season may experience influenza.[2] In addition, school-aged children spread influenza to other schoolchildren, family members, and members of the community.[3,4] However, many children do not receive vaccinations or do not follow the recommended dose regimen,[4,5–7] despite the fact that immunization is one of the most

Correspondence: Jean-Eric Tarride
PATH Research Institute, 25 Main Street West, Suite 2000, Hamilton, ON L8P 1H1, Canada
Tel +1 9 055 237 284 ext 5282
Fax +1 9 055 220 568
Email tarride@mcmaster.ca

effective and cost-effective ways to protect against influenza. There are currently two types of influenza vaccines available in Canada: intranasal live attenuated influenza vaccine, trivalent (LAIV; FLUMIST®; MedImmune, Gaithersburg, MD) and injectable trivalent inactivated influenza vaccine (TIV). Although LAIV is indicated for the prevention of influenza in Canadians aged between 2 and 59 years old,[8] the Canadian National Advisory Committee on Immunization recently stated that for healthy children and adolescents aged between 2 and 17 years old, "[a]vailable data indicates that LAIV would be preferred over TIV in this population, although the [National Advisory Committee on Immunization] recognizes that other programmatic considerations will impact the implementation of this recommendation in publicly funded programs."[9] To help inform decision makers about the relative value of LAIV, the study objective was to determine the cost-effectiveness of LAIV and TIV in healthy Canadian children and adolescents.

Methods

Study overview

A cost-effectiveness model[10] comparing LAIV and TIV in children aged 24–59 months was supplemented by primary (ie, a survey of 144 Canadian physicians) and secondary (eg, literature) data to model three age cohorts of Canadian children: 2–5 years of age, 6–9 years of age, and 10–17 years of age. Extrapolation of these results to healthy children aged 2–17 years old was conducted using Canadian age distribution statistics from Statistics Canada.[11] In the absence of dominance (ie, one alternative being less costly and more effective than the other alternative), the results were reported in terms of incremental cost per quality-adjusted life year (QALY) gained, as per the recommendations of the current Canadian guidelines for economic evaluations.[12] Univariate and probabilistic analyses were conducted, and both a Ministry of Health perspective and a societal perspective were considered. All costs were expressed in 2010 dollars and the model was built in Microsoft® Excel (1997-2003 Microsoft Excel, Microsoft Corporation, Redmond, WA).

Model structure and time horizon

As shown in Figure 1, children can develop vaccine-related adverse events (AEs) following the administration of LAIV or TIV (eg, fever, runny nose, sore arm). In both cases (no AEs or AEs), two outcomes are possible: no influenza or influenza. Influenza can present as either uncomplicated influenza, influenza with acute otitis media (AOM), influenza with lower respiratory infections (LRI), or influenza with AOM and LRI. Children could survive or die following influenza. As children are vaccinated against influenza with either LAIV or TIV, the basic structure of the two treatment arms was similar. A 12-month time horizon was used in the analysis to capture all costs and outcomes associated with an influenza episode.

Vaccine effectiveness

The efficacy of LAIV and TIV was taken from the re-analysis[10] (and MedImmune LLC, data on file, 2007) of a large head-to-head double-blind randomized trial comparing LAIV and TIV in children aged 6–59 months (the Belshe et al trial),[13] to determine the relative efficacy of LAIV in children aged 24–59 months. Results indicated that among those children aged 24–59 months who developed influenza (4.90% and 10.46% of those vaccinated with LAIV and TIV, respectively), the vast majority had uncomplicated influenza (4.30% in the LAIV group and 8.64% in the TIV group), while a small proportion experienced influenza with AOM (0.23% and 1.00% for the LAIV and TIV arms, respectively), or influenza with LRI (0.37% and 0.82% for the LAIV and TIV arms, respectively)[10] (and MedImmune LLC, 2007). Since recent evidence surrounding LAIV suggests there is no difference in efficacy in healthy children by age or circulating influenza subtype,[14,15] it was assumed that the relative efficacy of LAIV compared with TIV was similar in the three age groups.

Since the severity of influenza may change depending on age group and in the absence of Canadian primary and secondary data for children aged older than 5 years, 144 Canadian physicians were surveyed to estimate the breakdown of influenza by age group in terms of: (1) uncomplicated influenza, (2) influenza with AOM, (3) influenza with LRI and (4) influenza with AOM and LRI. As a reference point, physicians were provided with the values used by Belshe et al[13] for children aged 2–5 years old (ie, 82%–88% of all influenza episodes were uncomplicated influenza). Physicians were asked to validate these estimates for children aged 2–5 years old and to provide an estimate for the two other age groups (ie, 6–9 years of age and 10–17 years of age). The resulting influenza breakdown was applied to the overall efficacy of LAIV and TIV for each age group assuming no differences in severity of influenza between arms, as shown in Table 1. The probabilities of vaccine-related AEs (medically significant wheezing [MSW] occurring within 42 days following vaccination, injection-site reactions, and reactogenicity events occurring within 10 days following

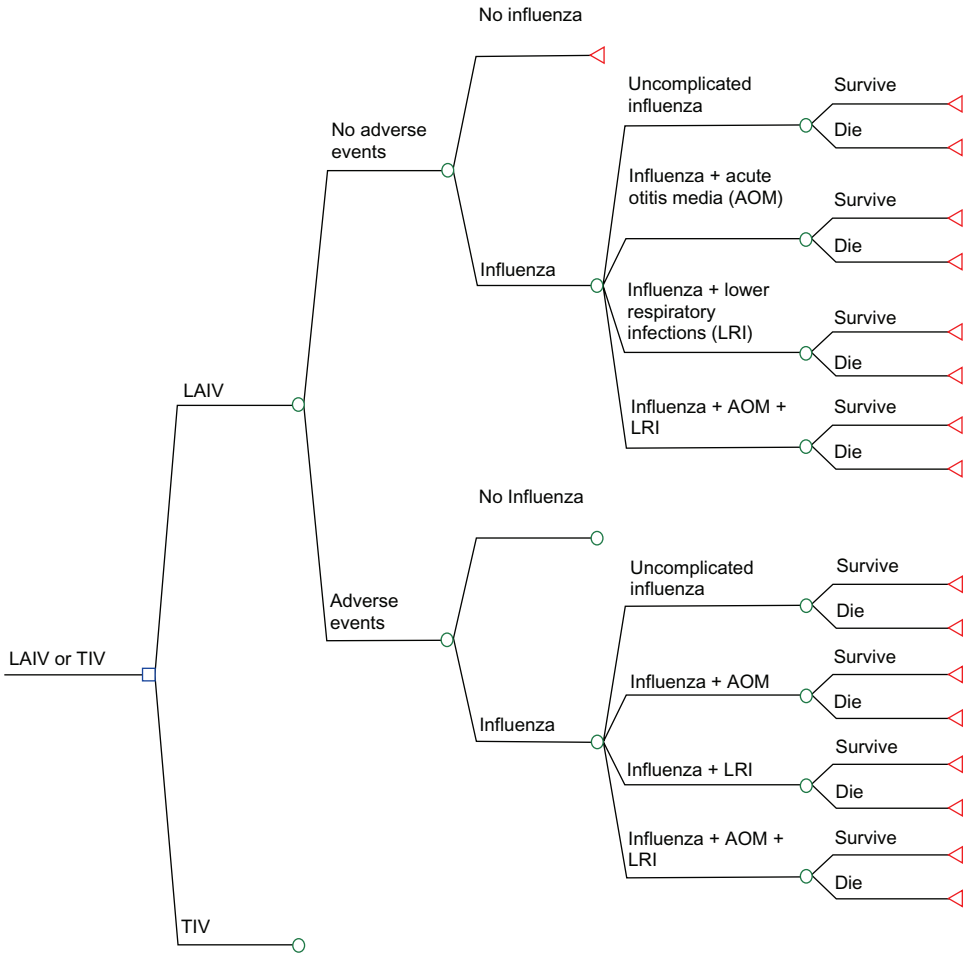

Figure 1 Model structure.
Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; AOM, acute otitis media; LRI, lower respiratory infections.

vaccination) and influenza-related mortality (0.0001% for uncomplicated influenza and influenza with AOM, and 0.0025% for influenza + LRI and influenza + AOM + LRI) were taken from the re-analysis[10] (and MedImmune LLC, 2007) of the trial conducted by Belshe et al.[13] These results were adjusted for the two other age groups, assuming that the rate of influenza in children older than 5 years of age was similar between treatment arms. Contrary to Luce et al,[10] AEs related to the injection site only were assumed to be 0 for LAIV (vs 5.35% in Luce et al[10]), while AEs related to runny or stuffy nose only were set at 0 for TIV (vs 7.5% in Luce et al[10]). Since MSW is unlikely to occur in older children, we assumed a zero probability of MSW in children aged 10–17 years old. To reflect that the AEs related to the influenza vaccination decrease with age, injection site events for older children were adjusted based on the study conducted by Prosser et al (Table 1).[16] For example, Prosser et al[16] assumed that the probability of an injection-site reaction decreased from 0.0025 in children aged 2–5 years old to 0.001 in children aged 5–11 years old, and to 0.0003 in children aged 12–17 years old.

Calculations of QALYs

On a scale from 0 (death) to 1 (perfect health), the model attributes utilities of 0.558 to uncomplicated and complicated influenza,[17] 0.851 to MSW,[18] and 0.9333 to noninfluenza or to a nonwheezing period,[19] as per Luce et al.[10] The average number of symptom days was derived from the Belshe et al trial[13] (4.03 for uncomplicated influenza, 11.06 for complicated influenza, and 12.78 for MSW), and this information was applied across the three age groups. To calculate QALYs, utilities were weighted by time spent in health states (eg, number of symptom days).[20] As an illustration, the average annual QALYs associated with influenza were calculated as: [0.558 (ie, utility of influenza) × 4.03 days (average number of days with uncomplicated influenza)] + [0.933 (ie, utility

Table 1 Clinical probabilities

Variable	Age 2–5 years			Age 6–9 years			Age 10–17 years		
	LAIV	TIV	Data source	LAIV	TIV	Data source	LAIV	TIV	Data source
Probability of uncomplicated or complicated influenza	4.9%	10.5%	Luce et al[10] and MedImmune (data on file, 2007)	4.9%	10.5%	Assumption based on Belshe et al[14] and Rhorer et al[15]	4.9%	10.5%	Assumption based on Belshe et al[14] and Rhorer et al[15]
Breakdown of influenza									
Uncomplicated influenza	67%	67%	Physician survey	72%	72%	Physician survey	75%	75%	Physician survey
Influenza + AOM	12%	12%	Physician survey	9%	9%	Physician survey	6%	6%	Physician survey
Influenza + LRI	14%	14%	Physician survey	13%	13%	Physician survey	13%	13%	Physician survey
Influenza + AOM + LRI	7%	7%	Physician survey	6%	6%	Physician survey	6%	6%	Physician survey
Vaccine-associated adverse events									
Medically significant wheezing	2.1%	2.5%	MedImmune (data on file, 2007)	2.1%	2.1%	MedImmune (data on file, 2007) assuming same value for LAIV and TIV	0.0%	0.0%	Assumption
Injection site events*	22.5%	33.8%	MedImmune (data on file, 2007)	9.0%	11.1%	Based on MedImmune (data on file, 2007) and adjusted for age using Prosser et al[16] (age 5–11)	2.7%	3.3%	Based on MedImmune (data on file, 2007) and adjusted for age using Prosser et al[16] (age 12–17)
Reactogenicity events†	50.0%	33.7%	MedImmune (data on file, 2007)	16.0%	13.0%	Based on MedImmune (data on file, 2007) and adjusted for age using Prosser et al[16] (age 5–11)	4.8%	3.9%	Based on MedImmune (data on file, 2007) and adjusted for age using Prosser et al[16] (age 12–17)

Notes: *Defined as injection site only (assumed 0 for LAIV) + injection site and runny/stuffy nose + injection site and other reactogenicity + injection site, runny/stuffy nose, and other reactogenicity; †defined as runny/stuffy nose only (assumed 0 for TIV) + other reactogenicity only + runny/stuffy nose and other.

Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; AOM, acute otitis media; LRI, lower respiratory infections.

without influenza) × 361.22 days (average number of days with no influenza)]. Similar calculations were used to calculate the QALYs associated with MSW and complicated influenza.

Resource utilization and unit costs

The model considers resource utilization and costs incurred by the Ministry of Health (eg, vaccine-, AE-, and influenza-related costs). To reflect a societal perspective, indirect costs incurred by parents (eg, over-the-counter medications, transportation costs, and the cost of lost days of work or usual activities performed by parents due to the children's vaccination or influenza episodes) were also analyzed. The probabilities of office visits were calculated by multiplying the rates of MSW, as well as the rates of complicated and uncomplicated influenza (as given in Table 1) by the corresponding number of physician visits, which were derived from the physician survey (Table 2). The probabilities of influenza-related hospitalizations for LAIV and TIV across each age group were calculated using Canadian data from the Sebastian et al study,[21] and were applied to the Belshe et al trial (MedImmune, 2007).[13]

In the absence of Canadian data, the probability that children aged 2–5 years old would undergo hospitalizations following MSW was taken from Luce et al[10] and applied to the other age groups, assuming equal rates between treatment arms. Furthermore, the length of stay associated with hospitalizations, the proportion of emergency room (ER) visits due to influenza or MSW, as well as medical management of influenza and MSW, were also taken from Luce et al's[10] study. To calculate the amount of time lost by caregivers, our panel of physicians was asked to estimate the proportion of medical visits across each age group in which at least one parent accompanied their child (ie, 100% of the time for the children aged 2–9 years old and 75% of the time for the older age group), as well as the percentage of office visits in which the children attended strictly to receive the influenza vaccine (ie, 32% of the time). The model assumed that only one parent would accompany the children, and it was identified that the parent who always attended these consultations was the mother. Canadian data were used to identify the proportion of mothers who were employed full-time (54%), part-time (19%), and to calculate the average transportation costs spent to travel to the physician's office (CAD$1.32).[22–24] Time lost from work (full time worker) or from usual activities (mother not working) due to vaccination was only applied when the purpose of the visit was only to receive an influenza vaccination as determined by the physicians. Time lost due to an influenza episode was based on the number of febrile

Table 2 Resource utilization

Variable	Age 2–5 years			Age 6–9 years			Age 10–17 years		
	LAIV	TIV	Data source	LAIV	TIV	Data source	LAIV	TIV	Data source
Office visit probabilities									
MSW	5.16%	6.11%	Physician survey (2.4 visits per episode) applied to Belshe et al trial[13]	4.30%	4.30%	Physician survey (2.0 visits per episode) applied to Belshe et al trial[13]	0%	0%	Assumption
Uncomplicated influenza	6.88%	14.72%	Physician survey (2.1 visits per episode) applied to Belshe et al trial[13]	7.05%	15.07%	Physician survey (2.0 visits per episode) applied to Belshe et al trial[13]	6.60%	14.13%	Physician survey (1.8 visits per episode) applied to Belshe et al trial[13]
Influenza + AOM	1.35%	2.89%	Physician survey (2.3 visits per episode) applied to Belshe et al trial[13]	0.79%	1.70%	Physician survey (1.8 visits per episode) applied to Belshe et al trial[13]	0.41%	0.88%	Physician survey (1.4 visits per episode) applied to Belshe et al trial[13]
Influenza + LRI	1.58%	3.37%	Physician survey (2.3 visits per episode) applied to Belshe et al trial[13]	1.34%	2.86%	Physician survey (2.1 visits per episode) applied to Belshe et al trial[13]	1.27%	2.72%	Physician survey (2.0 visits per episode) applied to Belshe et al trial[13]
Influenza + AOM + LRI	0.72%	1.54%	Physician survey (2.1 visits per episode) applied to Belshe et al trial[13]	0.50%	1.07%	Physician survey (1.7 visits per episode) applied to Belshe et al trial[13]	0.41%	0.88%	Physician survey (1.4 visits per episode) applied to Belshe et al trial[13]
Hospitalization probabilities (%)									
MSW	0.0914%	0.1820%	Luce et al[10]	0.0914%	0.0914%	Same value for CAIV and TIV – lower value	0%	0%	Assumption
Uncomplicated influenza	0.0004%	0.0008%	Sebastian et al[21] applied to Belshe et al trial[13]	0.0001%	0.0003%	Sebastian et al[21] applied to Belshe et al trial[13]	0.00001%	0.00003%	Sebastian et al[21] applied to Belshe et al trial[13]
Influenza + AOM	0.0004%	0.0008%	Sebastian et al[21] applied to Belshe et al trial[13]	0.0001%	0.0003%	Sebastian et al[21] applied to Belshe et al trial[13]	0.00001%	0.00003%	Sebastian et al[21] applied to Belshe et al trial[13]
Influenza + LRI	0.0001%	0.0002%	Sebastian et al[21] applied to Belshe et al trial[13]	0.00003%	0.0001%	Sebastian et al[21] applied to Belshe et al trial[13]	0.000003%	0.00001%	Sebastian et al[21] applied to Belshe et al trial[13]
Influenza + AOM + LRI	0.0001%	0.0002%	Sebastian et al[21] applied to Belshe et al trial[13]	0.00003%	0.0001%	Sebastian et al[21] applied to Belshe et al trial[13]	0.000003%	0.00001%	Sebastian et al[21] applied to Belshe et al trial[13]
Average length of hospital stay									
MSW	5.00	5.55	Luce et al[10]	5.00	5.00	Luce et al[10]	0.00	0.00	Luce et al[10]
Uncomplicated influenza	2.20	2.20	Luce et al[10]	2.20	2.20	Luce et al[10]	2.20	2.20	Luce et al[10]
Influenza + AOM	2.20	2.20	Luce et al[10]	2.20	2.20	Luce et al[10]	2.20	2.20	Luce et al[10]
Influenza + LRI	2.80	2.80	Luce et al[10]	2.80	2.80	Luce et al[10]	2.80	2.80	Luce et al[10]
Influenza + AOM + LRI	2.80	2.80	Assume values for influenza + AOM	2.80	2.80	Assume values for influenza + AOM	2.80	2.80	Assume values for influenza + AOM

Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; MSW, medically significant wheezing; AOM, acute otitis media; LRI, lower respiratory infections.

days observed in the Belshe et al trial,[13] which was assumed to be similar between treatment arms and older age groups (ie, from 3.00 days to uncomplicated influenza to 3.52 days for influenza + AOM).

The cost per dose of LAIV (CAD$14.00) was provided by the manufacturer, while the weighted average cost of a dose of TIV was calculated at CAD$9.59 based on IMS Drugstore and Hospital sales for January 2010 (data on file, AstraZeneca Canada). Costs related to the administration of the vaccine were taken from Sanders et al,[25] while other costs were derived from public sources in Ontario or Canada (Table 3). For children with previous vaccinations (37% and 42% for children aged 2–5 and 6–9 years old, respectively, as per the results of the physician survey), it was assumed that one dose of LAIV or TIV would be administered. It was also assumed that two doses of the vaccine were to be given to all children with no previous influenza vaccination. As per the guidelines of the Canadian Paediatric Society, children aged 9 years or older were assumed to receive one dose of the vaccine.[26]

Table 3 Unit costs

	Cost (CAD$)	Source
Vaccine-related costs (per dose)		
LAIV	$14.00	AstraZeneca (data on file)
TIV	$9.59	AstraZeneca based on IMS data (data on file)
Administration of LAIV	$3.59	Sander et al[25]
Administration of TIV	$3.59	Sander et al[25]
Proportion previously vaccinated		
Age 2–5 years	37%	Physician survey
Age 6–9 years	42%	Physician survey
Age 10–17 years	100%	Canadian guidelines[26]
Influenza-related direct costs		
Hospitalization for influenza		
Age 2–5	$3228.76	CIHI; OHIP schedule of benefits and fees[27,28]
Age 6–9	$3465.77	CIHI; OHIP schedule of benefits and fees[27,28]
Age 10–17	$3465.77	CIHI; OHIP schedule of benefits and fees[27,28]
ER visit for influenza, AOM, or LRI	$232.77	OHIP schedule of benefits and fees; OCCI[28,29]
Office visit for an adverse event, influenza, AOM, or LRI	$42.35	OHIP schedule of benefits and fees[28]
Direct nonmedical cost		
Transportation costs	$1.32	National Resource Canada[23] and Canadian Automobile Association[24]
Indirect costs		
Cost of lost day of work or usual activities	$173.28	Statistics Canada[30]

Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; CIHI, Canadian Institute for Health Information; ER, Emergency room; OCCI, Ontario Case Costing Initiative; AOM, acute otitis media; LRI, lower respiratory infections; OHIP, Ontario Health Insurance program.

Incremental cost-effectiveness analyses

The base case scenario evaluates the cost-effectiveness of vaccinating children for the first time with LAIV as opposed to TIV, taking into account that approximately 63% of children aged 2–5 years old have never been vaccinated for influenza, as per the physician survey. Three age groups were modeled and the results were extrapolated to healthy children aged between 2 and 17 years old using Statistics Canada data on Canadian age distribution.[11] As of July 1, 2008, out of 6,206,814 Canadian children aged between 2 and 17 years old, 23% were aged 2–5 years old (1,417,525) and 23% were aged 6–9 years old (1,442,144). Children aged 10–17 years old accounted for 54% of this population (3,347,145). These percentages were used to calculate the expected costs and benefits of vaccinating children aged 2–17 years old. The base case analysis did not include any benefits derived from the prevention of influenza transmission within a household resulting from vaccinating children against influenza.

In a secondary analysis, we evaluated the impact of including secondary wild-type influenza virus transmission among household members. In this scenario, it was assumed that 18% of contacts per influenza case contracted influenza.[31] Time lost by each parent (either from work or from performing their usual daily activities) due to influenza transmitted from the child was also considered in this scenario.

Univariate and probabilistic sensitivity analyses

Variables tested in univariate sensitivity analyses included, but were not limited to, the relative risk reduction of LAIV versus TIV (from 70% to 30%; base case: 54%); the price of TIV vaccine (from CAD $9.59 to $7); the percentage of children requiring two doses (ranging from 0% to 100%); and all unit costs (±20% of the base case costs). Probabilistic analyses in which all parameters for LAIV and TIV were varied simultaneously according to specified distributions were conducted using Monte Carlo techniques. According to good modeling practices,[32] beta distributions were used to represent the uncertainty associated with probabilities (eg, the probability of developing MSW) or utilities. Gamma distributions and trimmed normal distributions were used for the cost and length of stay data, respectively. Both the beta and gamma distributions were fitted by the method of moments.[32] Table 4 presents the characteristics

Table 4 Distributions used for the probabilistic sensitivity analyses

	LAIV				TIV			
	Mean value	**Distribution**	**Alpha**	**Beta**	**Mean value**	**Distribution**	**Alpha**	**Beta**
Influenza								
Uncomplicated influenza	3.28%	Beta	95	2803	7.01%	Beta	193	2565
Influenza + AOM	0.59%	Beta	5	843	1.26%	Beta	22	1725
Influenza + LRI	0.68%	Beta	25	3599	1.46%	Beta	25	1656
Influenza + AOM + LRI	0.34%	Beta	25	7249	0.73%	Beta	25	3362
Vaccine-associated adverse events								
MSW	2.1%	Beta	47	2140	2.5%	Beta	56	2142
Injection-site events	22.5%	Beta	19	66	33.8%	Beta	16	32
Reactogenicity events	50.0%	Beta	12	12	33.7%	Beta	16	32
Office visit probabilities								
MSW	5.16%	Beta	50	928	6.11%	Beta	59	904
Influenza + AOM	6.88%	Beta	91	1237	14.72%	Beta	85	493
Influenza + AOM	1.35%	Beta	10	723	2.89%	Beta	44	1466
Influenza + LRI	1.58%	Beta	17	1053	3.37%	Beta	33	956
Influenza + AOM + LRI	0.72%	Beta	0	0	1.54%	Beta	0	0
Hospitalization probabilities								
MSW	0.0914%	Beta	25	27,287	0.1820%	Beta	25	13,687
Uncomplicated influenza	0.0004%	Beta	25	6,308,360	0.0008%	Beta	25	2,949,493
Influenza + AOM	0.0004%	Beta	25	6,308,360	0.0008%	Beta	25	2,949,493
Influenza + LRI	0.0001%	Beta	25	26,893,702	0.0002%	Beta	25	12,574,320
Influenza + AOM + LRI	0.0001%	Beta	25	26,893,702	0.0002%	Beta	25	12,574,320
Average length of hospital stay								
MSW	5.00	Trimmed normal (5.00; 1)			5.55	Trimmed normal (5.00; 1.11)		
Uncomplicated influenza	2.20	Trimmed normal (2.20; 0.44)			2.20	Trimmed normal (2.20; 0.44)		
Influenza + AOM	2.20	Trimmed normal (2.20; 0.44)			2.20	Trimmed normal (2.20; 0.44)		
Influenza + LRI	2.80	Trimmed normal (2.20; 0.56)			2.80	Trimmed normal (2.20; 0.56)		
Influenza + AOM + LRI	2.80	Trimmed normal (2.20; 0.56)			2.80	Trimmed normal (2.20; 0.56)		
Unit costs (CAD$)								
LAIV cost	$14.00	Gamma	25	1				
TIV cost	$9.59	Gamma	25	0.4				
Administration costs	$3.59	Gamma	25	0.1				
Hospitalization	$3641.59	Gamma	1	3642				
ER visit	$221.39	Gamma	25	9				
Physician visit	$42.35	Gamma	25	2				
Transportation costs	$1.32	Gamma	25	0.1				
Cost of lost day of work	$173.28	Gamma	25	7				
Utility data								
Noninfluenza and nonwheezing period	0.93	Beta	6	0.4				
MSW	0.85	Beta	14	2				
Influenza	0.56	Beta	44	35				

Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; MSW, medically significant wheezing; AOM, acute otitis media; LRI, lower respiratory infections; ER, emergency room.

of the distributions used in the probabilistic sensitivity analyses for the main study parameters. When measures of dispersion were not available, the following conventions were used to fit the distributions used in the probabilistic sensitivity analyses. Standard errors were assumed to be 20% of the mean values associated with proportions (eg, influenza) and unit costs other than hospitalization costs (eg, drug costs). Standard errors were assumed to be 100% of the mean hospitalization costs and 10% for the utility data. A total of 1000 simulations were conducted and the uncertainty associated with the parameters was represented using cost-effectiveness acceptability curves.[32] It should be noted that the uncertainty associated with the effectiveness of the vaccines was not incorporated by fitting a distribution to the relative effectiveness of LAIV when compared with TIV, but rather by varying the effectiveness of each vaccine. As such, different distributions were assigned to LAIV and TIV (Table 4).

Table 5 Costs results*

	Age 2–5 years			Age 6–9 years			Age 10–17 years			Age 2–17 years		
	LAIV	TIV	Difference	LAIV	TIV	Difference	LAIV	TIV	Difference	LAIV	TIV	Difference
Vaccination costs												
Vaccine acquisition	$22.82	$15.63	$7.19	$22.12	$15.15	$6.97	$14.00	$9.59	$4.41	$17.89	$12.25	$5.64
Vaccine administration	$5.85	$5.85	$0.00	$5.67	$5.67	$0.00	$3.59	$3.59	$0.00	$4.58	$4.58	$0.00
Adverse-event costs	$12.87	$16.76	–$3.89	$8.78	$8.72	$0.06	$0.60	$0.58	$0.02	$5.30	$6.17	–$0.87
Total vaccination costs	$41.54	$38.24	$3.30	$36.57	$29.54	$7.03	$18.19	$13.76	$4.43	$27.78	$23.01	$4.77
Influenza costs												
Outpatient costs	$5.46	$11.68	–$6.22	$5.11	$10.94	–$5.83	$4.69	$10.03	–$5.34	$4.96	$10.61	–$5.66
ER costs	$2.17	$4.64	–$2.47	$1.99	$4.26	–$2.27	$1.79	$3.83	–$2.04	$1.92	$4.11	–$2.19
Hospitalization	$0.04	$0.08	–$0.04	$0.01	$0.02	–$0.01	$0.00	$0.00	$0.00	$0.01	$0.02	–$0.01
Prescription drug costs	$0.97	$2.08	–$1.11	$0.98	$2.10	–$1.12	$0.99	$2.11	–$1.12	$0.98	$2.10	–$1.12
Total influenza costs	$8.64	$18.48	–$9.84	$8.09	$17.32	–$9.23	$7.47	$15.97	–$8.50	$7.88	$16.86	–$8.98
Total direct health care costs	$50.18	$56.72	–$6.53	$44.68	$46.86	–$2.18	$25.66	$29.73	–$4.07	$35.67	$39.88	–$4.20
Over the counter medications	$0.49	$1.05	–$0.56	$0.49	$1.05	–$0.56	$0.49	$1.05	–$0.56	$0.49	$1.05	–$0.56
Transportation costs	$0.87	$1.06	–$0.19	$0.82	$0.99	–$0.17	$0.54	$0.69	–$0.15	$0.68	$0.84	–$0.16
Cost of time lost from work	$33.10	$53.26	–$20.16	$32.62	$51.75	–$19.13	$22.26	$41.29	–$19.03	$27.14	$46.45	–$19.31
Cost of time lost from usual activities	$22.19	$33.78	–$11.59	$21.82	$32.81	–$10.99	$14.33	$25.27	–$10.94	$17.86	$28.96	–$11.10
Total indirect costs	$56.65	$89.15	–$32.50	$55.75	$86.60	–$30.85	$37.62	$68.30	–$30.68	$46.17	$77.30	–$31.14
Total societal costs	$106.83	$145.87	–$39.03	$100.43	$133.46	–$33.03	$63.28	$98.03	–$34.75	$81.84	$117.18	–$35.34

Note: *All amounts in Canadian dollars.

Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; ER, emergency room.

Results

Due to the increased efficacy of LAIV compared with TIV in preventing influenza in children, the additional cost of LAIV was offset by the decrease in costs associated with AE management, outpatient physician visits, ER visits, and hospitalizations for all age groups (Table 5). Indirect costs were also reduced with LAIV. In terms of outcomes (Table 6), vaccinating 100,000 healthy children aged 2–17 years old with LAIV instead of TIV was estimated to gain 34 QALYs. Vaccinating these children was also found to prevent around 5500 cases of influenza, 10,000 physician visits, 1000 ER visits, and 17,500 days lost of which 11,500 were the equivalent of full -time days lost from work (Table 6).

When a reduction in secondary transmission of the wild-type virus to household contacts was modeled across all age groups, LAIV was associated with additional cost savings when compared to TIV. From a societal perspective, the savings increased from CAD$39.03 to CAD$56.77 for children aged 2–5 years old, from CAD$33.03 to CAD$50.77 for children aged 6–9 years old, and from CAD$34.75 to CAD$52.48 for children aged 10–17 years old. The results of other univariate sensitivity analyses indicated that these results were robust against changes in the price differential between LAIV and TIV, and robust against changes in relative risk reductions associated with LAIV versus TIV. The results also held up against other model assumptions (Figure 2).

The results of the probabilistic sensitivity analyses are shown in Figure 3, which presents the cost-effectiveness acceptability curves. Results indicated that if society was willing to pay CAD$50,000 per QALY (societal perspective), the probability of LAIV being cost-effective was 0.96 for children aged 2–5 years old, 0.92 for children aged 6–9 years old, and 0.94 for children aged 10–17 years old. At CAD$100,000 per QALY, these probabilities increased to close to 1 for all age groups. Similarly, from a Ministry of Health perspective, the probability of LAIV being cost-effective for all direct health care costs was almost 1 for all age groups at commonly accepted thresholds (Figure 3).

Discussion

Similar to the previous US cost-effectiveness analysis of LAIV versus TIV administration in children aged 2–5 years old,[10] the results of this study indicated that LAIV was the dominant influenza vaccination strategy used in healthy children aged 2–5 years old from both a societal and a Ministry of Health perspective. LAIV was also found to be the dominant strategy for the other two age groups and for Canadian children aged 2–17 years old, despite the fact that

Table 6 Clinical outcome results per 100,000 vaccinated children

	Age 2–5 years			Age 6–9 years			Age 10–17 years			Age 2–17 years*		
	LAIV	TIV	Difference	LAIV	TIV	Difference	LAIV	TIV	Difference	LAIV	TIV	Difference
QALYs	93,262	93,224	37	93,264	93,229	34	93,271	93,238	33	93,267	93,233	34
All episodes of influenza	4893	10,464	–5572	4893	10,464	–5572	4893	10,464	–5572	4,893	10,464	–5572
Uncomplicated influenza	3278	7011	–3733	3523	7534	–4011	3669	7,848	–4179	3,546	7583	–4038
Influenza + AOM	587	1256	–669	440	942	–501	294	628	–334	395	844	–450
Influenza + LRI	685	1465	–780	636	1,360	–724	636	1,360	–724	647	1,384	–737
Influenza + AOM + LRI	342	732	–390	294	628	–334	294	628	–334	305	652	–347
Hospitalizations	92	184	–92	92	92	0	0	0	0	42	64	–21
ER visits	1097	2322	–1,225	1,022	1,996	–975	770	1,646	–877	903	1882	–979
Outpatient visits	15,687	28,633	–12,947	13,971	24,986	–11,015	8699	18,605	–9906	11,519	22,379	–10,861
Total days lost	19,684	38,003	–18,319	19,567	36,954	–17,387	15,192	32,493	–17,301	17,232	34,787	–17,555

Notes: *The results for the 2–17 years age group were extrapolated from the other three age groups using Canadian age distributions statistics. As such, this column is not additive of the three other columns.
Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; QALYs, quality-adjusted life years; AOM, acute otitis media; LRI, lower respiratory infections; ER, emergency room.

conservative assumptions were used when extrapolating the results observed in the Belshe et al trial[13] to an older population of healthy children. When all model parameters were simultaneously varied, the results of the probabilistic analyses indicated that the probability of LAIV being cost-effective in comparison to TIV was almost one at commonly accepted thresholds (eg, CAD$50,000 and CAD$100,000 per QALY gained). When secondary transmission was modeled, LAIV provided additional benefits at a lower cost. Although we did not include this scenario as our base case analysis to provide a more conservative estimated benefit, recent Canadian data suggest that these protective effects may be even larger than those anticipated in our analyses.[33] Similarly, other potential benefits of LAIV were not modeled, such as increased vaccination compliance due to LAIV needle-free administration,[34] substantial efficacy following a single dose in previously unvaccinated young children,[35,36] and an approximate efficacy rate of 60% through a second influenza season without revaccination.[37]

Several limitations were associated with this study. In comparing LAIV and TIV, the study relied on a large randomized controlled trial of primarily healthy children and it is not known how these results apply to children with asthma or wheezing. However, it is very unlikely that the results would change significantly given that similar relative efficacy results were observed in young children with a history of recurrent respiratory tract illnesses and in older children and adolescents with asthma.[38,39] We also assumed that the relative efficacy of LAIV compared with TIV was similar across age groups. Although this assumption was supported for LAIV, as per recent analyses of LAIV evidence,[14,15] we assumed the same for TIV in a conservative approach.

In the absence of head-to-head trials in older healthy children, data regarding the rates of other outcomes following

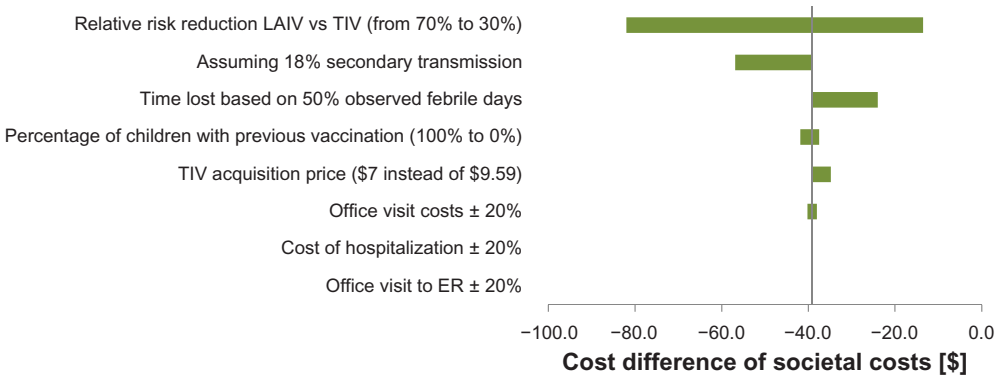

Figure 2 Tornado diagram (societal perspective, children aged 2–5 years old – savings of CAD$39.00 in the base case analysis).
Abbreviations: LAIV, intranasal live attenuated influenza vaccine; TIV, injectable trivalent inactivated influenza vaccine; ER, emergency room.

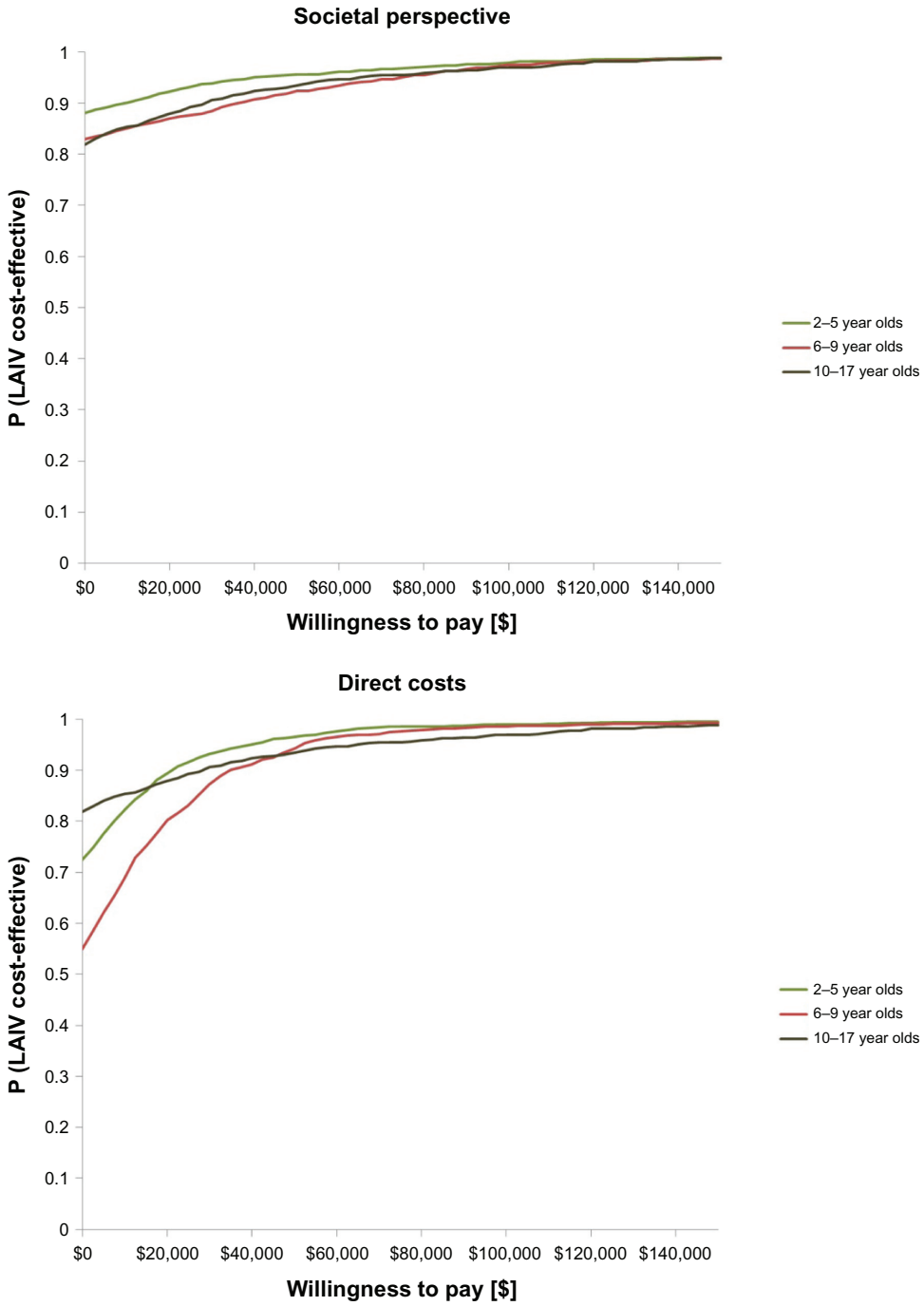

Figure 3 Cost-effectiveness acceptability curves.
Abbreviation: LAIV, intranasal live attenuated influenza vaccine.

influenza in children aged 24–59 months old were sometimes used to model the two other age groups. To mitigate the impact of this assumption, we always assumed equality between the two treatments. In addition, sensitivity analyses decreasing the relative efficacy of LAIV when compared to TIV in all age groups indicated that LAIV was still the dominant strategy (from a societal perspective) even when the efficacy rate was reduced to 30% (as compared with 54%). Noncompliance to vaccination schedules for children aged less than 9 years old was not modeled, although this is a frequent problem in real life. However, this assumption should not adversely affect the relative efficacy of LAIV compared with TIV, as LAIV has shown high efficacy following a single dose in previously unvaccinated children.[15,36]

Although we did not include secondary transmission of influenza in the base case analysis, LAIV was found to

provide additional benefits at a lower cost when secondary transmission was modeled; however, the model structure used in our analysis (ie, the decision tree) cannot fully deal with the spread of disease between individuals. The use of transmission models characterizing the population as being susceptible to infection, being infected, or being infectious to others is an important avenue of research to evaluate the cost-effectiveness of influenza vaccines. We did not model a "no vaccination" strategy; rather, we used data from a head-to-head trial comparing two vaccines.

It should also be noted that this trial was conducted during the 2004–2005 influenza season, which was a mild to moderate influenza season. As such, the results may not be generalizable to severe influenza seasons. In the absence of pediatric utility data, we followed the approach used by Luce et al,[10] which was to use adult utility values as proxy. Although utility data derived from a pediatric population is the preferred option when modeling populations of children and adolescents, changing the utility values associated with no influenza, influenza, or MSW should not affect the overall conclusion (eg, more QALYs generated with LAIV).

Finally, a value of information analysis was not conducted to determine if there would be value in conducting additional research to reduce the remaining uncertainty associated with the results. However, this situation is unlikely since the results of the probabilistic sensitivity analyses indicated that the probability of LAIV being more cost-effective than TIV was almost one at commonly cited thresholds. In addition, the results of the sensitivity analyses indicated that LAIV was still cost saving, even when the relative risk reduction of LAIV compared with TIV was decreased from 70% to 30% (Figure 2).

Despite these limitations, this study also had several strengths. First, the study used data from a large head-to-head randomized trial comparing LAIV and TIV in children aged 2–5 years old and conservative assumptions were used when it was necessary to extrapolate the results to older children. Second, we surveyed 144 Canadian physicians to estimate several key variables not available from the literature (eg, number of physician visits). The large number of physicians answering the survey and the variety of their geographical locations provided a good representation of the treatment of influenza in Canadian primary care practices. Finally, to take into account the uncertainty associated with key model parameters, we conducted a probabilistic analysis as well as several univariate sensitivity analyses; in all scenarios, LAIV was still the dominant strategy.

In conclusion, vaccinating Canadian children between the ages of 2–17 years old with LAIV instead of TIV was found to be the dominant strategy from both a societal and a Ministry of Health perspective.

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Disclosure

The authors report no conflicts of interest in this work.

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