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Cost-effectiveness of live attenuated influenza vaccine versus inactivated influenza vaccine among children aged 24–59 months in the United States

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ABSTRACT

Background: The US Advisory Committee on Immunization Practices (ACIP) recently expanded the influenza vaccine recommendation to include children 24–59 months of age. In a large head-to-head randomized controlled trial, live attenuated influenza vaccine, trivalent (LAIV) demonstrated a 54% relative reduction in culture-confirmed influenza illness compared with trivalent inactivated influenza vaccine (TIV) among children aged 24–59 months.
Objective: To evaluate the relative cost and benefit between two influenza vaccines (LAIV and TIV) for healthy children 24–59 months of age.
Methods: Using patient-level data from the clinical trial supplemented with cost data from published literature, we modeled the cost-effectiveness of these two vaccines. Effectiveness was measured in quality-adjusted life years (QALY) and cases of influenza avoided. The analysis used the societal perspective.
Results: Due to its higher acquisition cost, LAIV increased vaccination costs by $7.72 per child compared with TIV. However, compared with TIV, LAIV reduced the number of influenza illness cases and lowered the subsequent healthcare use of children and productivity losses of parents. The estimated offsets in direct and indirect costs saved $15.80 and $37.72 per vaccinated child, respectively. LAIV had a net total cost savings of $45.80 per child relative to TIV. One-way and probabilistic sensitivity analyses indicated that the model was robust across a wide range of relative vaccine efficacy and cost estimates.
Conclusions: Due to its increased relative vaccine efficacy over TIV, LAIV reduced the burden of influenza and lowered both direct health care and societal costs among children 24–59 months of age.

1. Introduction

Seasonal influenza epidemics are estimated to cause 300,000 hospitalizations and 36,000 excess respiratory deaths annually in the US [1–3]. While most of the influenza-related morbidity and mortality occurs in the elderly, young children are hospitalized for influenza-attributable illnesses at rates similar to the elderly [3–5]. Further, influenza attack rates are highest among children, with attack rates ranging from 23% to 48% during inter-pandemic years [1,6,7]. Because children shed viruses longer than older cohorts, they are considered a major source of influenza transmission to the community, particularly to household members [6,8,9].

In July 2006, the US Advisory Committee on Immunization Practices (ACIP) expanded its immunization recommendation for influenza to include children 24–59 months of age. A key reason for expanding the recommendation to the 24–59-month age group was because of the increased risk for influenza-associated clinic and emergency department visits in this age cohort [10].

Vaccination against influenza remains the most efficient way of preventing influenza illnesses. Currently, there are two influenza vaccines available in the US, live attenuated influenza vaccine, trivalent (LAIV) and inactivated influenza vaccine, trivalent (TIV). LAIV is currently licensed in the US for administration to eligible individuals aged 2–49 years and TIV is indicated for eligible individuals aged

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6 months and older. In children younger than 5 years of age, LAIV is not recommended for those with recurrent wheezing, asthma, and other high-risk medical conditions because of insufficient safety data in these populations. However, more than 80% of children aged 24–59 months are eligible to receive LAIV [11,12].

Numerous clinical trials have shown LAIV to have a high vaccine efficacy in pediatric populations [11,13–17]. Three head-to-head pediatric trials comparing LAIV with TIV have shown significantly lower rates of culture-confirmed influenza illness with LAIV regardless of the match between the vaccine and circulated influenza strains [11,13,15]. The first was a randomized, open label study of LAIV versus TIV that enrolled 2187 children 6–71 months of age with a history of recurrent respiratory tract infections. The overall relative efficacy of LAIV against all strains regardless of antigenic match was 52% (95% CI: 25–71) [13]. A second study was a randomized, open label, active-controlled efficacy and safety study of LAIV versus TIV in children 6–17 years of age with a history of asthma. The relative efficacy of LAIV compared with TIV was 32% (95% CI: 1–54) against all strains regardless of antigenic match [15]. The Ashkenazi et al. [13] and Fleming et al. [15] head-to-head studies were conducted in Europe and Israel during the 2002–2003 influenza season; this season was classified as mild and the vaccine was well matched to the dominant circulating strains, which were influenza B [18]. In addition, these clinical trials enrolled special pediatric populations, some of whom are not within the current recommended population for LAIV.

The third study was the pivotal randomized, double-blind, multinational study designed to evaluate the safety and efficacy of LAIV compared with TIV in children less than 5 years of age (Comparative Efficacy Study) [11]. Among children aged 24–59 months, there was a 54% relative reduction (95% CI: 42–65). The Comparative Efficacy Study was conducted during the 2004–2005 influenza season; this season is described as a mild-to-moderate influenza season [19] with a noted mismatch between the vaccine and the late-circulating, predominant A/H3N2 wild-type influenza virus [20]. Due to its large sample size among the indicated population for both vaccines, the 24–59-month cohort from the Comparative Efficacy Study served as the basis for the cost-effectiveness analysis presented in this paper.

Prior economic analyses examining the impact of influenza vaccination among infants and young children compared vaccination against no vaccination [7,21–27]. To the best of our knowledge, only one study indirectly compared the cost-effectiveness of LAIV relative to TIV [27]. However this analysis preceded the results from the Comparative Efficacy Study and did not include parental productivity losses associated with time lost from work or usual activities to care for sick children, which is encouraged by The Panel on Cost-Effectiveness in Health and Medicine [28].

The purpose of the present economic evaluation is to assess the cost-effectiveness of LAIV relative to TIV in preventing influenza in children aged 24–59 months based on the results of the Comparative Efficacy Study. Given the higher efficacy and higher acquisition cost of LAIV, understanding the cost-effectiveness of these vaccines is needed to inform vaccine providers, policy bodies, public and private formulary decision-makers, and payers regarding influenza vaccine policy for children.

2. Methods

2.1. Model overview

We conducted a cost-effectiveness analysis of influenza vaccination modeling LAIV versus TIV in children aged 24–59 months in the United States. A simplified diagram of the model structure is provided in Fig. 1 and describes the combination of clinical events that can occur when vaccinating children against influenza. The model pathways consider the type of vaccine received, occurrence of vaccine-associated adverse events, episodes of uncomplicated and complicated influenza (i.e. influenza with acute otitis media (AOM) or lower respiratory infection (LRI)), and incidence of mortality. To calculate costs, we determined the probability of vaccinated children experiencing each clinical event (e.g. influenza, adverse event) as well as the probability and average amount of associated resource use (e.g. vaccine administration, influenza hospitalization, prescription antiviral treatment). Using a probability-weighted approach, the average number of units of each resource used per vaccinated child was multiplied by each resource's corresponding unit cost value to arrive at the cost per vaccinated child. Quality-adjusted life year (QALY) losses were calculated based on the probability-weighted average number of life years lost due to mortality and time spent in a reduced health state due to symptoms of influenza or an adverse event.

Data for children aged 24–59 months in the Comparative Efficacy Study were used to populate model pathways, clinical outcomes, and resource use parameters. To ensure comparability between the benefit and risk probabilities used in the economic analysis, the clinical trial safety cohort data was used as the sole data source (LAIV, $n = 2187$; TIV, $n = 2198$). Supplemental data for parameters that could not be obtained from the trial were collected from the published literature.

In accordance with the Panel on Cost-Effectiveness in Health and Medicine [28], the model assumes the societal perspective (e.g. direct and indirect costs). The model follows children over the course of a single influenza season (defined as the period from first vaccination of the season to 180 days following final vaccination). This time horizon captures vaccine-related expenditures and relevant clinical outcomes and corresponds to the timeframe used in the Comparative Efficacy Study.

2.2. Influenza and its complications

Influenza was defined as the presence of culture-confirmed influenza-like illness defined by the Centers for Disease Control and Prevention (CDC-ILI) modified to be age appropriate for young children [11] that occurred during the influenza surveillance period (November through May) caused by community-acquired wild-type strains (herein referred to as influenza). This definition requires fever $\geq$37.8 °C (100 °F) oral or equivalent plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days. Since resource use is affected by influenza-related complications, the model classified influenza as complicated if there was documented acute otitis media (AOM) or lower respiratory infection (LRI) within 7 days before or 14 days after the onset of the influenza. All other cases of influenza were considered uncomplicated. AOM was defined as a health care provider diagnosis of AOM concurrent with fever $\geq$37.8 °C (100 °F) oral or equivalent and associated with the use of antibiotics. LRI was defined as health care provider-confirmed shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, or croup.

Probabilities for uncomplicated and complicated influenza, hospitalizations, and outpatient physician visits are presented in Table 1 [5,11,27,29–31]. No influenza mortality was observed in the Comparative Efficacy Study; however, it has been observed in population-based studies of pediatric influenza and is an important clinical outcome. Therefore, the model incorporated expected rates of mortality due to influenza based on estimates reported in the published literature for uncomplicated and complicated influenza among children aged 24–59 months (Table 1).

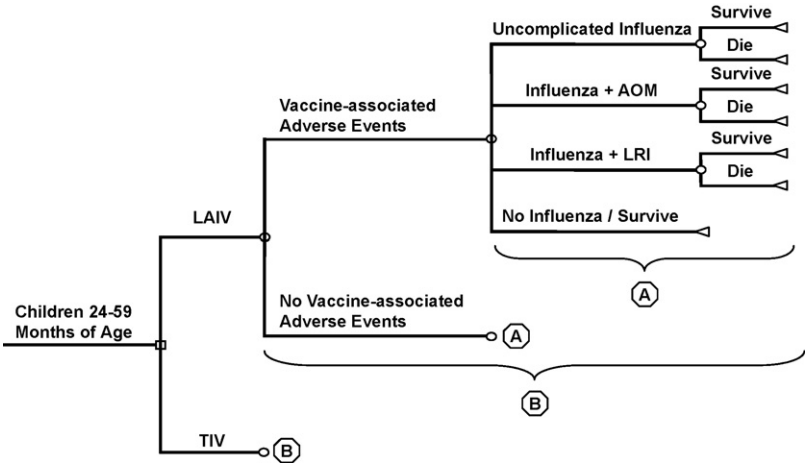

Fig. 1. Model structure. (A) Represents the same event branches illustrated for vaccine-associated adverse events. (B) Represents the same event branches illustrated for LAIV. AOM: acute otitis media; LAIV: live attenuated influenza vaccine, trivalent; LRI: lower respiratory infection; TIV: trivalent inactivated influenza vaccine.

2.3. Vaccine efficacy

The vaccine efficacy used in each arm of the model was derived from a post hoc analysis of the Comparative Efficacy Study for children aged 24–59 months. The base case model used the probability of uncomplicated influenza for the LAIV and TIV arms of 4.30% and 8.64%, respectively. For complicated influenza (i.e. influenza + AOM, influenza + LRI) in the LAIV arm, the probabilities were 0.23% and 0.37%, respectively. For TIV, the probabilities for influenza + AOM and for influenza + LRI are 1.00% and 0.82% (Table 1).

LAIV resulted in a significant relative reduction in influenza cases compared with TIV (54.4% relative reduction; 95% CI: 41.8–64.5). For one-way sensitivity analysis, the relative reduction ranged from 40% to 60% while holding constant the probability of influenza infection for TIV.

Table 1
Clinical probabilities and resource utilization[a]

Model parameter	LAIV	TIV
Probability of uncomplicated and complicated influenza (%)[b]		
Uncomplicated influenza	4.30	8.64
Influenza + AOM	0.23	1.00
Influenza + LRI	0.37	0.82
Vaccine-associated adverse events (%)		
MSW	2.15	2.55
Reactogenicity event	50.0	41.2
Injection site event	27.8	33.8
Probability of outpatient physician visit (%)		
MSW	2.38	2.78
Uncomplicated influenza	4.30	8.64
Influenza + AOM	0.46	2.00
Influenza + LRI	0.78	1.55
Probability of hospitalization (%)[c]		
MSW	0.09	0.18
Uncomplicated influenza	0.02	0.04
Influenza + AOM	0.02	0.04
Influenza + LRI	0.00	0.01
Hospital length of stay (d)[d]		
MSW	5.00	5.55
Uncomplicated influenza	2.20	2.20
Influenza + AOM	2.20	2.20
Influenza + LRI	2.80	2.80

Mortality	Value	References
Uncomplicated influenza	6.6×10^{-6}	[11,27,31]
Influenza + AOM	6.6×10^{-6}	[11,27,31]
Influenza + LRI	1.676×10^{-4}	[11,27,31]

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

[a] Except where indicated, all data were based on post hoc analysis of the 24–59-month age cohort from the Comparative Efficacy Study.

[b] Children were considered to have one of two forms of complicated influenza: influenza plus AOM or influenza plus LRI; no children had influenza plus AOM plus LRI. Cases were classified as complicated if the recorded date of AOM or LRI occurred within 7 days before or 14 days after the recorded date of the influenza. All other cases of influenza were considered uncomplicated.

[c] Refs. [5,27,29].

[d] Ref. [30].

2.4. Vaccine-associated adverse events

Medically significant wheezing (MSW) occurring within 42 days following vaccination and reactogenicity or injection site events occurring within 10 days following vaccination were the only adverse events included in the model, because there were no significant differences between vaccination arms for any of the other adverse events reported in the trial. Incidence rates for adverse events reported in Table 1 reflect the probability of adverse events per vaccinated child. MSW was defined as the presence of wheezing on a physical examination conducted by a health care provider, with a new prescription for daily bronchodilator therapy; respiratory distress; or oxygen saturation <95%. While there was no statistically significant difference in the incidence of MSW between children receiving LAIV (2.15%) and TIV (2.55%), this adverse event was included to understand its impact on cost-effectiveness via sensitivity analysis. Reactogenicity events included runny nose, sore throat, and cough. Injection site events included pain, redness, or swelling at the site of injection (Table 1).

2.5. Costs

Costs were categorized as vaccination costs, influenza direct costs, and influenza indirect costs. Vaccination costs included direct medical costs (i.e. vaccine acquisition, administration, and adverse event costs), direct non-medical costs (i.e. transportation costs), and indirect costs (i.e. caregiver time lost from work and usual activities attributable to vaccination and adverse events). Influenza direct costs included costs for hospitalizations, emergency room visits, office visits, prescription and over-the-counter (OTC) medications, as well as transportation costs related to cases of influenza. Influenza indirect costs consisted of caregiver

Table 2
Costs

	Cost ($)	Range ($)	References
Vaccine-related costs (per dose)			
LAIV	17.95	–	[32]
TIV	11.20	10.00–14.00	[32]
Administration of LAIV	9.90	–	[33]
Administration of TIV	9.90	–	[33]
Adverse event-related costs (per episode)			
MSW	62.92	62.46–63.39	[11,29,34–38,41] (CPT Code 99213)
Reactogenicity	1.81	–	[39], OTC medication
Injection site reaction	1.81	–	[39], OTC medication
Influenza-related direct costs			
Hospitalization for influenza	7056	1818–8247	[40]
ER visit for influenza, AOM, or LRI	188	163–212	[38] (CPT Code 99283)
Office visit for an adverse event, influenza, or AOM	77	67–86	[38] (CPT Code 99213)
Office visit for LRI	116	102–130	[38] (CPT Code 99214)
Direct non-medical costs			
Transportation costs	5.75	–	[24]
Indirect costs			
Cost of lost day of work or usual activities	218	–	[42], civilian workers: employer costs

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

time lost from work and usual activities attributable to cases of influenza. Costs are presented in Table 2 [11,24,29,32–42] and have been adjusted to 2006 US$, when necessary, using the medical care services component of the consumer price index [43].

2.6. Vaccine costs

For determining vaccination costs, costs were applied to the percentages of children needing two doses in the trial (69.4% of children aged 24–59 months were influenza vaccine naive) versus one dose [11]. Administration costs for LAIV and TIV were assumed to be equivalent and were based on the average reimbursement to pediatricians for administering childhood vaccinations [33]. Physician fees for office visits (and corresponding transportation and indirect costs) were assumed to occur for each vaccine-associated adverse event.

2.7. Outpatient costs

Based on the clinical trial by Ashkenazi et al. [13], children with symptomatic culture-confirmed influenza had on average 2.2 unscheduled office visits per case. In contrast, Salo et al. [44] assumed 1 office visit per case and Prosser et al. [27] assumed 0.47 office visits per case in their economic analyses. Using the midpoint of these estimates, it was assumed that children with uncomplicated influenza had, on average, 1 office visit each. For children with complicated influenza, visits for AOM or LRI were considered additional to the visit for influenza.

2.8. Hospital and emergency room costs

Since hospitalization data from the trial was uncommon and not influenza specific, the model relied on hospitalization rates and average length of stay for primary cases of influenza derived from published literature [5,27]. Average hospital length of stay for cases of influenza were based on the Healthcare Cost and Utilization Project data [30]. Emergency room (ER) visits for influenza or MSW were not collected in the trial. To calculate the frequency of ER visits, a ratio of office visits to ER visits (for influenza) was applied to the probability of an influenza office visit and a ratio of hospitalizations was applied to ER visits (for MSW) to calculate the probability of hospitalization for MSW [29,45].

Because fever was required for identification of symptomatic influenza cases, caregiver time lost due to influenza was equated to the average number of febrile days owing to culture-confirmed influenza observed in the Comparative Efficacy Study. Caregiver time lost because of MSW was based on estimates reported by Stevens and Gorelick [46] (Table 3) [11,47–49].

2.9. Quality-adjusted life years and utilities

Table 3 presents the utilities for each health state other than death (utility = 0) considered in the analysis. Because most reactogenicity and site of injection events related to influenza vaccination are of short duration and mild severity, the only adverse event considered in the QALY calculations was MSW. The proportion of time spent in the MSW and influenza health states was based on the weighted average number of symptom (MSW) or febrile days (influenza) observed in the trial (Table 3). To determine the average number of life years remaining after accounting for the estimated premature deaths due to influenza, the model assumed a life expectancy of 77.9 years [50]. Because life years are accumulated over time, remaining life years were discounted using a 3% discount rate.

Table 3
Health state utilities and duration

Input	Value	Source
Health state utility		
No influenza; no wheezing	0.933	48
MSW	0.851	49
Influenza (uncomplicated and complicated)	0.558	47
Average number of febrile days		
Uncomplicated influenza	3.00	11
Influenza + AOM	3.52	11
Influenza + LRI	3.33	11
Average number of symptom days		
MSW	12.78	11

AOM: acute otitis media; LRI: lower respiratory infection; MSW: medically significant wheezing.

Table 4
Total and incremental average costs per vaccinated child

	LAIV cost ($) (95% CI)	TIV cost ($) (95% CI)	Difference[a] cost ($) (95% CI)
Vaccination costs			
Vaccine acquisition	30.40 (30.40–30.40)	18.97 (17.22–21.31)	11.43 (9.09–13.18)
Vaccine administration	16.76 (16.76–16.76)	16.76 (16.76–16.76)	0.00 (0.00–0.00)
Adverse event costs	6.15 (3.06–8.05)	8.06 (5.35–10.36)	−1.91 (−2.32 to −2.26)
Transportation costs	4.64 (4.59–4.75)	4.70 (4.63–4.85)	−0.06 (−0.11 to −0.04)
Indirect costs	51.85 (49.47–54.88)	53.59 (51.21–56.63)	−1.74 (−1.74 to −1.74)
Total vaccination costs	109.80 (104.83–112.93)	102.09 (96.99–106.26)	7.72 (4.98, 9.08)
Influenza direct costs			
Outpatient costs	7.69 (6.43–9.02)	16.71 (14.99–18.72)	−9.02 (−11.23 to −6.92)
ER costs	0.92 (0.51–1.64)	2.02 (1.16–3.51)	−1.11 (−1.95 to −0.63)
Hospitalization costs	2.86 (0.06–11.42)	6.20 (2.79–15.02)	−3.34 (−3.90 to −2.08)
Medication costs	1.59 (1.27–1.99)	3.50 (2.96–4.13)	−1.90 (−2.50 to −1.36)
Transportation costs	0.35 (0.29–0.42)	0.77 (0.69–0.87)	−0.42 (−0.51 to −0.33)
Total influenza direct costs	13.41 (9.60–22.06)	29.21 (24.70–37.68)	−15.80 (−18.85 to −12.69)
Influenza indirect costs			
Time lost from work	19.46 (1.24–63.51)	41.99 (4.22–130.81)	−22.53 (−68.69 to −2.41)
Time lost from usual activities	13.13 (0.84–42.84)	28.32 (2.85–88.23)	−15.19 (−46.33 to −1.63)
Total influenza indirect costs	32.59 (2.07–106.35)	70.31 (7.07–219.04)	−37.72 (−115.02 to −4.04)
Grand total average cost	155.81	201.61	−45.80

ER: emergency room; LAIV: live attenuated influenza vaccine, trivalent; TIV: trivalent inactivated influenza vaccine. *Note*: Because of rounding, columns and rows may not sum exactly to the total amounts presented in the table.

[a] Negative numbers indicate cost savings for LAIV.

2.10. Analyses

The primary effectiveness measure selected in this study was the average number of QALYs gained per vaccinated child. Secondary effectiveness measures included the number of vaccinated children avoiding influenza, AOM, LRI, hospitalizations, ER visits, and outpatient physician visits per 100,000 vaccinated children. The total average cost of care per vaccinated child was the main economic outcome. The cost-effectiveness measure selected for this economic analysis was the incremental cost per (additional) QALY gained. This incremental cost-effectiveness ratio was calculated as the difference in the total average costs of care associated with each vaccination arm divided by the difference in QALYs gained. Trial data were analyzed using SAS (SAS Institute, Cary, NC). All other analyses were conducted using Microsoft Excel™ (Microsoft, Redmond, WA). The model was validated internally by the study team and externally by an independent health economics consultant.

One-way sensitivity analyses were conducted to identify the primary sources of sensitivity in the model's estimation of treatment costs and outcomes associated with LAIV relative to TIV. In sensitivity analyses, we also explored the impact of including secondary wild-type influenza virus transmission among household members using the data from Hayden et al. [51]. In this study, 18% of contacts per influenza case contracted influenza. Therefore, we assumed that 18% of household contacts of trial participants with breakthrough cases would also contract wild-type influenza. We did not model influenza transmission outside of the household.

A probabilistic sensitivity analysis using Monte Carlo simulation was performed to evaluate the impact of simultaneous variation in clinical outcome and resource utilization parameters on the model conclusions. Probabilistic sensitivity analysis involves specifying distributions for model parameters to represent uncertainty in their estimation and employing Monte Carlo simulation to randomly sample from each of the parameter distributions and calculate the expected costs and clinical outcomes for that combination of parameter values. Parameter distributions were defined based on the means and standard deviations from the Comparative Efficacy Study and other source materials.

3. Results

The total average cost of care for children who received LAIV was $155.81 compared with $201.61 for children who received TIV, resulting in an estimated societal cost savings of $45.80 per child vaccinated with LAIV instead of TIV (Table 4). For every 100,000 children vaccinated, use of LAIV was projected to save approximately $4.6 million in societal costs compared with use of TIV. These savings were driven by lower influenza direct costs (LAIV, $13.41; TIV, $29.21) and lower influenza indirect costs (LAIV, $32.59; TIV, $70.31) due largely to the higher efficacy of LAIV. Vaccination costs were approximately $8 higher for children vaccinated with LAIV ($109.80) versus TIV ($102.09). Total and incremental costs for each cost component, with the associated 95% CIs, are presented in Table 4.

As the measure of primary effectiveness, an estimated 36 QALYs were gained for every 100,000 children vaccinated with LAIV instead of TIV. However, as is customary in cost-effectiveness analyses, the incremental cost per (additional) QALY gained was not calculated because LAIV resulted in lower costs and increased QALYs compared with TIV. For the secondary effectiveness measures, the estimated number of cases derived from the model for uncomplicated influenza, influenza with AOM, and influenza with LRI per 100,000 vaccinated children were 4346, 772, and 453 fewer cases for children vaccinated with LAIV compared with TIV, respectively (Table 5). Further, the number of hospitalizations, ER visits, and outpatient physician visits per 100,000 vaccinated children were estimated to be 138, 250, and 7058 fewer visits, respectively, for children vaccinated with LAIV compared with children vaccinated with TIV.

3.1. Sensitivity analysis

Table 6 depicts one-way sensitivity analysis for key variables. LAIV was cost-saving relative to TIV in each analysis. The model was most sensitive to the number of missed work days, which was based on the number of febrile days. Varying the number of missed work days between 1 and 7 days resulted in an estimated range

Table 5
Clinical outcomes measures per 100,000 vaccinated children

	LAIV	TIV	Difference
QALYs	93,267	93,230	36
Uncomplicated influenza	4,298	8,644	−4346
Influenza + AOM	229	1,001	−772
Influenza + LRI	366	819	−453
Hospitalizations	132	270	−138
ER visits	239	489	−250
Outpatient physician visits	7,910	14,968	−7058

ER: emergency room; LAIV: live attenuated influenza vaccine, trivalent; QALYs: quality-adjusted life years; TIV: trivalent inactivated influenza vaccine.

Table 6
Sensitivity analysis

Scenarios	Incremental cost ($)
Base case (direct and indirect costs)	−45.80
Direct costs are only considered	−15.80
Use thimerosal-free TIV cost ($14.00) as a comparator instead of thimerosal-containing TIV cost ($11.20)	−50.54
VFC acquisition price: LAIV ($17.65) vs. TIV ($8.65) instead of commercial prices	−41.99
All vaccinated children are naive instead of the observed naive rate (69.4%)	−43.73
All vaccinated children are not naive instead of the observed naive rate (69.4%)	−50.48
Assumed 18% secondary transmission of wild-type virus from influenza cases to household members	−70.72
Absenteeism based on 50% of observed febrile days	−26.94
Absenteeism, miss 1 day of work and/or usual activities	−26.81
Absenteeism, miss 7 days of work and/or usual activities	−84.42
Relative risk reduction from LAIV vs. TIV: 40% instead of the base case point estimate (54%)	−33.90
Relative risk reduction from LAIV vs. TIV: 70% instead of the base case point estimate (54%)	−60.66
Doubled MSW incidence rate in LAIV instead of the observed rate	−35.16
Halved MSW incidence of LAIV instead of the observed rate	−51.12
Assumed a mild influenza season (8% attack rate in unvaccinated children)	−8.97
Assumed a severe influenza season (40% attack rate in unvaccinated children)	−59.85

LAIV: live attenuated influenza vaccine, trivalent; MSW: medically significant wheezing; TIV: trivalent inactivated influenza vaccine; VFC: vaccines for children program. *Note*: All scenarios, other than the scenario "Direct costs are only considered" involve direct and indirect costs.

of cost saving in the LAIV arm of between $27 and $84 per child, respectively. Using a payer perspective (i.e. only direct costs are considered) rather than a societal perspective, LAIV saved $15.80 per child compared with TIV.

If a reduction in secondary transmission of wild-type virus to household members was incorporated, the cost savings due to LAIV increase to $70.72 compared with TIV. The model was also sensitive to changes in the relative vaccine efficacy of LAIV to TIV, vaccine acquisition price, average number of febrile days for complicated influenza, influenza attack rates, and percentage of children receiving two doses.

The results of the probabilistic sensitivity analysis are presented as a scatter plot in Fig. 2 and indicate that LAIV was associated with both increased QALYs and lower costs relative to TIV in 100% of the simulations.

4. Discussion

In recent years, there has been a growing national clamor for head-to-head trials to determine the comparative effectiveness and cost-effectiveness of alternative clinical options [52–62]. A conventional response to insufficient evidence of direct comparative effectiveness (and cost-effectiveness) is to engage in decision-analytic modeling [63]. However, such models struggle to combine and triangulate data from clinical trials, epidemiologic studies, beliefs about real-world clinical practice patterns, cost structures, and patient variables. Our analysis, using primarily data captured during a large head-to-head randomized controlled trial, provides direct comparative evidence on the cost-effectiveness of LAIV and TIV. We estimate that LAIV reduces direct and indirect healthcare costs and cases of influenza compared with TIV in the study population.

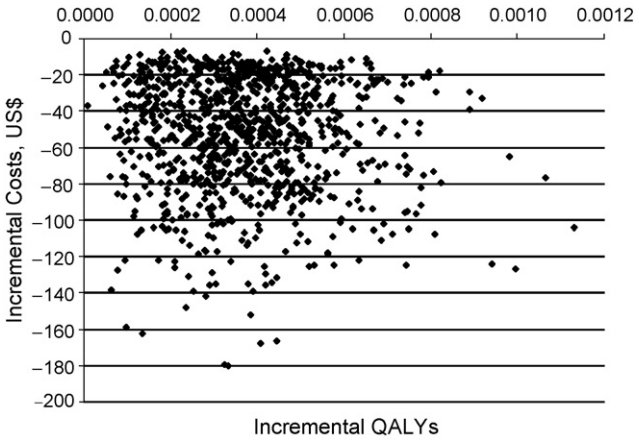

Fig. 2. Incremental costs and QALYs for LAIV vs. TIV. Points to the right of the *y*-axis indicate LAIV is more effective than TIV. Points below the *x*-axis indicate LAIV is less costly than TIV. LAIV: live attenuated influenza vaccine, trivalent; QALYs: quality-adjusted life years; TIV: trivalent inactivated influenza vaccine.

One previous economic analysis by Prosser et al. [27] addressed the comparative efficacy of these vaccines using an indirect evidence approach. This economic evaluation reported cost-effectiveness ratios (relative to no vaccination) for non-high-risk children aged 2 years of $15,000 (95% CI: cost savings to $180,000) per QALY for LAIV and $180,000 (95% CI: cost savings to $217,000) per QALY for TIV. While Prosser et al. did not have the benefit of having the results from the Comparative Efficacy Study, their analysis also suggests lower costs for LAIV compared to TIV. In contrast to the study by Prosser et al., our analysis also incorporated parental lost productivity associated with influenza. Similar to previous influenza vaccine economic analyses [21,24,25,44,64], we found that reductions in indirect costs are an important driver of influenza vaccine cost-effectiveness.

In our analysis, a number of conservative assumptions were made such as neglecting secondary transmission of wild-type influenza from children developing influenza to family members or others in the base case and using the price differential between the commercial prices of LAIV ($17.95 per dose) and thimerosal-containing multi-dose TIV ($11.20 per dose) rather than the preservative-free formulations of TIV ($14.00 per dose).

4.1. Limitations

The model has several limitations that should be acknowledged. First, the degree to which the study results are generalizable to populations different from those who participated in the Comparative Efficacy Study is not clear. In this large, multinational study, participants with history of wheezing were eligible to participate if they did not have history of "severe asthma or wheezing" or recent wheezing within the past 4 weeks [12].

The model does not account for partial compliance with the recommended two-dose regimen for children younger than 9 years of

age. The model was constructed according to the one- and two-dose regimens of the clinical trial, in which compliance rates were high. At the time the study was conducted, vaccine-naive children in the 24–59-month age group were supposed to receive two doses, while others were to receive one dose. However evidence suggests that compliance with two-dose regimens is low, ranging from 12% to 24% in children 2 years and older [65]. In placebo-controlled, clinical studies of previously unvaccinated children, LAIV demonstrated meaningful efficacy, approximately 60%, with a single dose [14,16,66]; this relative efficacy is lower than that seen with two doses of LAIV, but could still result in meaningful protection against illness. Studies with TIV have failed to demonstrate efficacy against influenza illness following a single dose [10,67–69]. Although the precise impact of partial compliance on cost and relative efficacy is unknown, we believe compliance effects would likely show greater cost savings of LAIV compared with TIV.

Approximately 69% of children in the trial received two doses of the vaccine. In accordance with this dosing pattern, the model estimated vaccination costs to be $11 higher per child for LAIV. This differential was attributable to LAIV acquisition costs which are approximately $7 higher per dose than TIV. In a real-world setting, because of increased pediatric vaccination in recent years, the percentage of children who are vaccine-naive and would require two doses would presumably be lower. This would decrease the vaccination cost differential.

Because the trial itself was not designed as an economic study, detail on QALYs, ER visits, influenza-specific hospitalizations, or influenza-specific outpatient visits were not available and had to be estimated from the scientific literature. To simplify the analysis, costs for telephone consultations, specialty provider visits, home health care visits, or durable medical equipment were not included.

The Comparative Efficacy Study did not include a placebo arm; therefore an economic analysis on the societal benefits of vaccinating all children 24–59 months of age was not estimated. In addition, a direct measure of the severity of the 2004–2005 influenza season was not captured in the trial. Because all children aged 6–59 months are currently recommend to receive annual influenza vaccine [10], the current model was undertaken to help decision-makers discern which vaccine may be the most appropriate option as that seems the most relevant question to address. The 2004–2005 influenza season was described as a mild-to-average year [19] with some degree of mismatch between the vaccine and circulating wild-type virus [20]. Although sensitivity analyses were conducted to examine the effect of various vaccine efficacies and influenza illness attack rates, the model results could differ for relative vaccine efficacies and influenza seasons with attack rates that vary outside the ranges tested.

5. Conclusion

Due in large part to higher efficacy, children vaccinated with LAIV had lower rates of influenza and correspondingly lower costs than children vaccinated with TIV. The analysis indicates that even with a $7 price premium over TIV, the value from a more efficacious influenza vaccine leads to reduced disease burden and increased worker productivity. Overall direct and indirect costs averaged $156 per child vaccinated with LAIV and $202 per child vaccinated with TIV.

We determined that because of the lower rates of influenza among children vaccinated with LAIV, 4346 cases of uncomplicated influenza and 1225 cases of complicated influenza can be avoided for every 100,000 children vaccinated with LAIV relative to TIV. The estimated cost savings amounts to $4.58 million for every 100,000 children vaccinated with LAIV relative to TIV.

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