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Cost Effectiveness of Influenza Vaccine Choices in Children Aged 2–8 Years in the U.S.

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Abstract

Introduction—Prior evidence found live attenuated influenza vaccine (LAIV) more effective than inactivated influenza vaccine (IIV) in children aged 2–8 years, leading CDC in 2014 to prefer LAIV use in this group. However, since 2013, LAIV has not proven superior, leading CDC in 2015 to rescind their LAIV preference statement. Here, the cost effectiveness of preferred LAIV use compared with IIV in children aged 2–8 years is estimated.

Methods—A Markov model estimated vaccination strategy cost effectiveness in terms of cost per quality-adjusted life year gained. Base case assumptions were: equal vaccine uptake, IIV use when LAIV was not indicated (in 11.7% of the cohort), and no indirect vaccination effects. Sensitivity analyses included estimates of indirect effects from both equation- and agent-based models. Analyses were performed in 2014–2015.

Results—Using prior effectiveness data in children aged 2–8 years (LAIV=83%, IIV=64%), preferred LAIV use was less costly and more effective than IIV (dominant), with results sensitive only to LAIV and IIV effectiveness variation. Using 2014–2015 U.S. effectiveness data (LAIV=0%, IIV=15%), IIV was dominant. In two-way sensitivity analyses, LAIV use was cost saving over the entire range of IIV effectiveness (0%–81%) when absolute LAIV effectiveness was >7.1% higher than IIV, but never cost saving when absolute LAIV effectiveness was <3.5% higher than IIV.

Conclusions—Results support CDC's decision to no longer prefer LAIV use and provide guidance on effectiveness differences between influenza vaccines that might lead to preferential LAIV recommendation for children aged 2–8 years.

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Introduction

Influenza causes 3,000–49,000 (23,607 average) U.S. deaths annually,¹ including 109 deaths among children in 2013–2014.² Before universal recommendations for U.S. influenza vaccination, influenza accounted for 10%–19% of office visits and 6%–29% of emergency department visits for acute respiratory illness or fever among children aged <5 years during influenza season.³ By other estimates, influenza resulted in seven to 12 additional outpatient visits per 100 children aged <15 years.⁴ Among individuals aged ≥19 years, influenza vaccination is estimated to have averted more than 2 million cases, nearly 900,000 medical visits, and about 10,000 hospitalizations since 2005.⁵

In addition to the inactivated influenza vaccine (IIV), given as an injection, live attenuated influenza vaccine (LAIV), given as a nasal spray, is licensed for use among children aged ≥2 years. Compared with IIV, LAIV is more costly and has a shorter shelf life. However, the practical advantage of LAIV over IIV is that needle-averse children may be more inclined to accept the nasal spray, resulting in higher vaccination rates. Also, meta-analyses and systematic reviews of influenza vaccine effectiveness previously showed that LAIV was more effective in preventing illness than IIV in children aged 2–8 years,^{6–9} and enhanced herd protection from LAIV was reported.¹⁰ By contrast, among older children, equivalent effectiveness for LAIV and IIV was demonstrated.⁷ These data led CDC in 2014 to state a preference for LAIV over IIV among children aged 2–8 years.⁷ However, this policy led to some controversy, owing to higher LAIV cost, live vaccine contraindications in some patient subgroups, and greater IIV availability.¹¹ In 2015, CDC changed this recommendation, expressing no preference for either vaccine, given more-recent U.S. data that did not confirm LAIV superiority and demonstrated relatively poor effectiveness of both vaccines against a drifted influenza A (H3N2) strain.¹²

Given these differences in vaccine type and controversy over recommending, then rescinding, preferred LAIV use in children aged 2–8 years, cost-effectiveness analysis (CEA) can illuminate the consequences of choosing one vaccine over another. Several CEAs of LAIV have been conducted using pre-2008 data, comparing LAIV with no vaccination.^{13–15} Only one CEA compared LAIV with IIV among U.S. children; however, it only included children aged 24–59 months and did not account for herd immunity effects.¹⁶

Here, two analyses examining influenza vaccination strategies in children aged 2–8 years are performed: the first with vaccine effectiveness as seen prior to the 2013–2014 influenza season, and the second with vaccine effectiveness as observed in the 2014–2015 season. In the first analysis, decision analytic cost-effectiveness modeling compared LAIV with IIV among children aged 2–8 years, commensurate with CDC's specific age criteria for their previous 2014–2015 LAIV preference policy,⁷ using published meta-analyses for vaccine effectiveness estimates.^{6,7} Because decision analysis typically cannot account for vaccination indirect (herd immunity) effects, epidemiological outputs from equation-based modeling and agent-based modeling incorporating these effects were added to the decision analysis model. The second set of analyses, because of recent data suggesting substantially reduced LAIV effectiveness for the 2013–2014 and 2014–2015 influenza A vaccine strains,¹⁷

investigated the favorability of LAIV vs. IIV over wider effectiveness ranges than those reported in prior meta-analyses.

Methods

A Markov state transition model estimated the cost effectiveness of influenza vaccination strategies in cohorts aged 2–8 years. The model, in monthly cycles, followed identical hypothetical cohorts over a 10-month time horizon (i.e., a single influenza season) from August through May. Two strategies were compared: preferential LAIV use versus IIV.⁷ Cohorts were assumed to have received at least two influenza vaccine doses in prior years, and hence only required a single vaccine dose during the modeled season.⁷ In the LAIV strategy, 11.7% of individuals aged 2–8 years had LAIV precautions or contraindications (asthma, immunosuppression, aspirin use, egg allergy⁷), and thus received IIV. Strategy effectiveness was measured in quality-adjusted life years (QALYs), to account for both time and quality of life, and in influenza cases prevented. Analyses took a societal perspective, following reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine,¹⁸ and were performed in 2014–2015.

In the Markov model (Figure 1), cohorts entered the model unvaccinated in August, and were vaccinated monthly based on total yearly influenza vaccine uptake multiplied by the average monthly influenza vaccination relative risk observed over the last 5 years (Appendix Figure 1).¹⁹ The risk and the consequences of influenza vaccination adverse events (wheezing and non-wheezing) were tracked within the vaccinated state. Each month, both the vaccinated and unvaccinated groups could become ill with influenza, based on the relative risk of influenza occurring in a given month (Appendix Figure 1), derived from observed incidence from the 2009–2010 through 2013–2014 influenza seasons,²⁰ multiplied by the CDC's estimated yearly influenza attack rate in the unvaccinated.²¹ Vaccinees' influenza infection risk was modified, beginning the month after vaccination, by the effectiveness of the received vaccine, with the monthly risk of influenza being the product of the derived monthly attack rate multiplied by one minus the risk of vaccine effectiveness. In all models, vaccine effectiveness was the effectiveness against all circulating influenza strains. Influenza complications (acute otitis media, wheezing, lower respiratory tract infections) and outcomes (hospitalization, death) were tracked within the influenza state. The model tracked only mortality due to influenza, assuming that other causes of death were not affected by vaccination. Influenza disease and influenza vaccination events were accounted for using the disutility (i.e., the loss of quality or duration of life) of those events. QALYs lost due to influenza mortality were discounted at 3% per year.¹⁸

It was also assumed that the relative risk of a given influenza case patient developing influenza complications was decreased by vaccination, with this risk being the same for both vaccines except for a diminution of acute otitis media risk with LAIV (relative risk=0.47, 95% CI=0.30, 0.73, based on a CDC meta-analysis).^{16,22,23} Influenza hospitalization risk and mortality were generally low and the same for both vaccines.

It was assumed that parent preference was not a factor in vaccine choice, and that coverage rates for LAIV or IIV strategies were equal. Only symptomatic influenza was modeled and,

in the base case analysis, no indirect (herd immunity) effects were modeled within the cohort aged 2–8 years. Assuming no indirect effects could bias the analysis against vaccination strategies or against vaccines with greater indirect effects. Possible indirect effects were examined in separate analyses outlined below.

Other parameter values used in the model are shown in Table 1. Influenza and influenza complication probabilities and utilities were obtained from a variety of literature and database sources, as noted. The yearly probability of influenza was derived from CDC estimates of influenza cases and averted cases in 2012–2013.²¹ Yearly influenza incidence for children aged 6 months to 4 years (28%) was used for the base case analysis; in a sensitivity analysis, results were examined when the incidence for those aged 5–19 (16%) was used because of the variability in incidence that occurs across seasons and age groups. Vaccine effectiveness was derived from multiple sources^{6,22} and was varied widely in sensitivity analyses. Influenza vaccination costs included vaccine costs derived from CDC vaccine price lists, private sector cost,²⁴ plus administration costs from Centers for Medicare and Medicaid and Medicaid Services data.²⁵

All parameter values were varied individually over the Table 1 ranges in one-way sensitivity analyses, and all parameters were varied simultaneously in a probabilistic sensitivity analysis, choosing randomly from distributions 5,000 times. Parameter distributions, which were used only for the probabilistic sensitivity analysis, were chosen based on data characteristics and parameter uncertainty: Probabilities and utilities were varied over beta distributions, costs used gamma distributions, relative risks were log normal distributions, and visit frequency data were Poisson distributions (Table 1). Probabilistic sensitivity analysis results are presented using a cost-savings threshold and a \$100,000 per-QALY-gained threshold. There is no U.S. cost-effectiveness criterion, but \$100,000 per QALY gained has become a commonly cited contemporary benchmark.^{26–28}

Indirect effects were estimated using influenza attack rate outputs derived from an equation-based dynamic transmission model and from an agent-based model, which both permit tracking of infection transmission among modeled populations. These models used similar input data to those used in the Markov model and identical exclusive use of LAIV and IIV strategies, creating monthly influenza incidence rates for children aged 2–8 years, which were then used as Markov model input data. The equation-based model (Appendix Figure 2) examined an age-structured synthetic population via a compartmental model similar to that described by Shim.²⁹ The agent-based model used the FRED software system³⁰ examined influenza spread, using the mean of three FRED runs, in a simulated population of Allegheny County, PA, with detailed demographic and geographic structure and household, school, and workplace contact networks.

The second set of analyses, prompted by recent variability in vaccine effectiveness, used wide effectiveness ranges, down to 0% effectiveness for either vaccine. Here, the between-vaccine differences needed for individual vaccine favorability were examined. In this analysis, LAIV versus trivalent IIV and LAIV versus quadrivalent IIV were also separately examined. Results were summarized in two-way sensitivity analyses, simultaneously

varying LAIV and IIV effectiveness, and examined using equation-based and agent-based models to account for indirect effects.

Results

Analysis Using Prior Vaccine Effectiveness

The Markov model predicted influenza disease risk in children aged 2–8 years of 20.4% with IIV use and 18.5% with LAIV use in the base case analysis, assuming 54.5% vaccination for both LAIV and IIV. CEA results are shown in Table 2. Per patient, the IIV strategy cost about \$9 more, owing to greater influenza illness costs, and was less effective than LAIV, resulting in an additional 0.00008 QALYs (about 0.7 hours) lost with IIV use. In the 2013 U.S. population of 28.4 million children aged 2–8 years,³¹ the base case model predicts that LAIV would avert 540,675 influenza cases and 206 influenza hospitalizations compared with IIV in this age group.

In one-way sensitivity analyses, varying each parameter individually over ranges suggested by prior meta-analyses, LAIV continued to be dominant (i.e., lower net cost and greater effectiveness) with variation of all but two parameters: LAIV effectiveness and IIV effectiveness. Specifically, the LAIV strategy was no longer dominant when LAIV effectiveness was 69.5% (base case value, 83%) or if IIV effectiveness was 76.5% (base case, 64%) when vaccine effectiveness values were individually varied. One-way sensitivity analyses using a \$100,000 per-QALY-gained threshold showed that LAIV was favored if its effectiveness was 66.9% or if IIV effectiveness was 79.7% (data not shown); IIV was favored if LAIV effectiveness was <68.0% or IIV effectiveness was 83.1% (data not shown). The relationship between vaccine effectiveness parameters, in light of recent low vaccine effectiveness levels, is further explored below.

The probabilistic sensitivity analysis, varying all parameters over their distributions when published meta-analysis vaccine effectiveness data were used, showed that LAIV was cost saving in 72% of the model iterations and was favored 78% of the time if a \$100,000 per-QALY-gained threshold was used. When influenza cases were examined as the outcome in a probabilistic sensitivity analysis, LAIV prevented more cases than IIV in 85.9% of the iterations.

The base case assumed a 28% influenza infection risk, which was derived from data for children aged 6 months to 4 years.³² Repeating analyses using a 16% influenza risk derived from data for children aged 5–19 years,³² LAIV was cost saving in 59% and was favored at a \$100,000/QALY threshold in 70% of model iterations.

Using the equation-based model influenza vaccination attack rate in the Markov model and vaccine uptake for LAIV=58.6% and IIV=57.9%, LAIV continued to be dominant in the CEA, with a 2.4% absolute risk reduction in influenza risk with LAIV (7.6% vs 10.0% with IIV). Using the agent-based model influenza attack rate, LAIV was again dominant, with an absolute influenza risk reduction of 3.8% (LAIV=14.6%, IIV=18.4%).

Analysis Using 2014–2015 Vaccine Effectiveness

In analyses incorporating 2014–2015 data and possible continuing vaccine ineffectiveness (LAIV=0%, IIV=15%¹²), IIV was dominant. In two-way sensitivity analyses (Figure 2), a complex pattern was found that varied based on vaccine effectiveness. If LAIV absolute effectiveness was >7.1% more than trivalent IIV, LAIV use, when compared to trivalent IIV use (Figure 2A), was cost saving and more effective over the entire range of IIV effectiveness (0%–81%). On the other hand, if LAIV's absolute effectiveness was <3.5% more than IIV, LAIV was never favored, using a cost savings threshold. As seen in Figure 2, the absolute effectiveness difference for LAIV to be favored increased as IIV effectiveness increased. Thus, if IIV effectiveness in children aged 2–8 years remains at its 2014–2015 level, 15%,¹² then LAIV would not be favored unless its absolute effectiveness was >4.1% more (i.e., LAIV effectiveness >19.1%); if IIV effectiveness returns to 64% (the meta-analysis derived value), LAIV absolute effectiveness would have to be >6.3% more (i.e., 70.3%) for LAIV to be favored. When quadrivalent IIV, with its greater cost (\$16.15, compared with \$10.69 for trivalent IIV), was considered (Figure 2B), LAIV was cost saving and more effective if its absolute effectiveness were >3.5% more throughout the IIV effectiveness range. These findings were confirmed when possible indirect effects were considered in equation- and agent-based models.

Discussion

Choosing LAIV versus IIV in children aged 2–8 year presents a conundrum. Prior meta-analyses suggest greater LAIV effectiveness in this group compared with IIV use, leading to a CDC policy favoring LAIV use in these children. However, the last two influenza seasons (2013–2014 and 2014–2015) showed no evidence of superior LAIV effectiveness and suggest LAIV inferiority compared with IIV. As a result, CDC now states no vaccine preference in children aged 2–8 years. Future vaccine effectiveness is uncertain, but should improve from the low levels recently observed.

These analyses support CDC policy decision making. Using the previous meta-analysis data^{6,9,23} that led to CDC favoring LAIV in children aged 2–8 years,⁷ LAIV use in this age group resulted in lower net costs for influenza vaccination and illness and lower influenza incidence compared with IIV. Model results were most sensitive to variation of vaccine effectiveness estimates; varying other parameters had little influence on results. Probabilistic sensitivity analyses, which varied all parameter values simultaneously, also favored LAIV over IIV. With recent evidence of lower LAIV effectiveness, these analyses also support the CDC's reversal of their policy favoring LAIV. If LAIV, the costlier vaccine, is not more effective than IIV and has similar uptake, then it will not be favored on clinical or economic grounds. However, if it does prove to be more effective in future years than IIV, it would also be less costly over the entire range of IIV effectiveness values if its absolute effectiveness was >7.1% more than trivalent IIV or >3.5% more than quadrivalent IIV.

Results using prior meta-analysis data are consistent with other CEAs.^{13–16} For instance, LAIV use in daycare settings saved \$5.47 per child in societal costs in a moderate attack-rate season.¹³ Among children aged 3–4 years not at high risk, LAIV and IIV had comparable cost-effectiveness ratios compared to no vaccination; this analysis did not

include LAIV's potentially greater effectiveness.¹⁵ Finally, in children aged 24–59 months old, LAIV saved \$15.80 in direct costs and \$37.72 in indirect costs per vaccinated child compared with IIV.¹⁶

The Markov model did not account for influenza vaccine herd immunity effects, likely underestimating population vaccination effects. To test the robustness of Markov model results, herd immunity effects were estimated using equation- and agent-based modeling, finding results similar to those of the original model, but with greater risk reduction observed, supporting the reliability of these results. This technique of cross-model validation could be considered for future vaccine CEAs.

Limitations

Prior CEAs could not assess the 2013–2014 CDC preference policy for children aged 2–8 years over the entire age range of that recommendation. The only CEA that directly compared LAIV and IIV in U.S. children addresses an incomplete age group (24–59 months), did not account for herd immunity effects, and was published in 2008.¹⁶ Decision analysis models lack the ability to capture the infectious disease transmission dynamics that other modeling techniques can. Influenza attack rate outputs from equation- and agent-based models were included, enhancing the robustness of these results.

All modeling efforts are only approximations of reality, with the value of their results based on their ability to capture some portion of reality. Here, models attempt to represent the impact of various vaccine policy options for decision making, but rely on data from a variety of sources, not necessarily data from gold standard randomized trials, which do not exist. Simplifying assumptions were made, such as the age-based risk of vaccination, to aid in the tractability of the modeling effort.

Only symptomatic infection was modeled in the Markov model. The issue of which influenza attack rates are most appropriate is quite complex and controversial; thus, sensitivity analyses were conducted. Use of parameter estimates outside the ranges of those in the sensitivity analyses may yield different results.

Quadrivalent LAIV is the only LAIV that has been used in the U.S. since the 2013–2014 influenza season; quadrivalent IIV is gradually being phased into use, but has only captured part of the IIV market thus far.³³ Quadrivalent IIV may be more effective than trivalent IIV vaccine, but minimal U.S. quadrivalent vaccine effectiveness data have been published to date. As with LAIV, future evidence of trivalent and quadrivalent IIV effectiveness, and their relative effectiveness compared with other vaccines, will determine their incremental cost effectiveness.

Conclusions

Markov decision analytic modeling enhanced by equation- and agent-based modeling of indirect effects and calibrated with older vaccine effectiveness data (i.e., showing greater LAIV effectiveness) found that preferred LAIV use compared with IIV use in children aged 2–8 years was likely to be cost saving, with improved influenza protection. This supported

the 2014–2015 CDC recommendations for preferential LAIV use in children aged 2–8 years. However, when more recent vaccine effectiveness was modeled (i.e., low LAIV effectiveness), IIV was favored. Thus, these results support the CDC decision to no longer prefer LAIV and provide guidance on what differences in effectiveness between vaccines result in LAIV being preferred, from both epidemiologic and economic standpoints, in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Markov model for influenza, its complications and vaccination.

Notes: Portions of the cohort can transition between health states based on monthly transition probabilities, represented by the arrows.

Figure 2.

Two-way sensitivity analysis – LAIV vs. IIV effectiveness, cost savings threshold in 2-8 year-olds.

Notes: The area where the live attenuated influenza vaccine (LAIV) is cost saving compared to the inactivated influenza vaccine (IIV) is depicted for hypothetical improved LAIV effectiveness values (y-axis) over IIV (x-axis). In panel (a), the trivalent IIV is considered; panel (b) considers the quadrivalent IIV.

Table 1**Parameter Values Used in the Model**

		Range			
	Base case	Low	High	Distribution	Reference
Probabilities					
Vaccine effectiveness					
IIV	64.0%	34.0%	81.0%	Beta	6,23
LAIV	83.0%	46.0%	91.0%	Beta	6
Vaccination adverse events					
Wheezing	2.6%	1.3%	3.8%	Beta	16
Hospitalized	0.18%	0.09%	0.27%	Beta	16
Other vaccine adverse event					
IIV	75.0%	50.0%	95.0%	Beta	16
LAIV	77.8%	50.0%	95.0%	Beta	16
LAIV contraindication	11.7%	11.1%	12.3%	Beta	34
Influenza attack rate (yearly, unvaccinated)	28.0%	17.0%	37.0%	Beta	21
Influenza complication risk					
Acute otitis media (AOM)					
No vaccination	15.0%	6.4%	27.3%	Beta	15,35
IIV	7.8%	3.9%	11.7%	Beta	16
Relative risk LAIV vs IIV	47.0%	30.0%	73.0%	Log Normal	23
Lower respiratory infection (LRI)					
Regardless of vaccine or vaccination status	7.6%	3.8%	11.4%	Beta	16
Hospitalization					
Influenza and influenza with AOM					
No vaccination	0.04%	0.02%	0.06%	Beta	16
Either vaccine	0.04%	0.02%	0.06%	Beta	
Influenza with LRI					
No vaccination	0.064%	0.032%	0.096%	Beta	36
Either vaccine	0.010%	0.005%	0.015%	Beta	16
Mortality					
Influenza and influenza with AOM	0.00066%	0.00033%	0.00099%	Beta	16
Influenza with LRI	0.017%	0.008%	0.025%	Beta	37
Costs and resource utilization					
Vaccination					
IIV cost	\$10.69	\$5.35	\$16.04	Gamma	6
LAIV cost	\$22.70	\$11.35	\$34.05	Gamma	6
Vaccine administration cost	\$25.08	\$19.08	\$32.32	Gamma	38
Adverse events					
Days of wheezing	12.78	6.39	19.17	Gamma	16

	Range			Distribution	Reference
	Base case	Low	High		
Wheezing cost	\$62.92	\$31.46	\$94.38	Gamma	16
Wheezing hospitalization cost	\$4,295	\$4,103	\$4,487	Gamma	39
Other adverse event costs	\$1.81	\$0.91	\$3.62	Gamma	16
Influenza illness					
Antiviral medication cost	\$103.00	\$51.50	\$154.50	Gamma	40
Office visit cost (per visit)	\$73.08	\$60.22	\$92.78	Gamma	38
Non-medical direct costs (per day)	\$162	\$81	\$243	Gamma	41
Hospitalization cost (per day)	\$2,140	\$1,748	\$2,532	Gamma	39
Influenza only					
Days ill	3.0	1.0	10.0	Gamma	16
Days hospitalized	2.2	1.0	7.0	Gamma	16
Probability of an office visit	40%	30%	50%	Beta	42
Office visits (if they occurred)	1	1	3	Poisson	
Acute otitis media					
Days ill	3.52	1	10	Gamma	16
Days hospitalized	2.2	1	7	Gamma	16
Probability of an office visit	100%	70%	100%	Beta	
Number of office visits	2	1	3	Poisson	
Medication cost	\$30	\$15	\$45	Gamma	43
Lower respiratory infection					
Days sick	3.33	1	10	Gamma	16
Days hospitalized	2.8	1	10	Gamma	16
Probability of an office visit	100%	70%	100%	Beta	
Number of office visits	2	1	3	Poisson	
Medication cost	\$30	\$15	\$45	Gamma	
Utility values					
Influenza utility	0.558	0.3	0.8	Beta	16
Wheezing utility	0.851	0.7	0.95	Beta	16
Disutility					
Non-wheezing adverse event (days lost)	0	0	1	Beta	16
Hospitalization (days lost)	2.8	1	10	Gamma	39
Death (quality adjusted years lost)	30.5	25.5	35.5	Gamma	44
Discount rate	3%	Not varied			

LAIV, Live attenuated influenza vaccine; IIV, inactivated influenza vaccine

Table 2

Cost-Effectiveness Analysis Results for LAIV vs. IIV, Using Previous Meta-Analysis Results for Vaccine Effectiveness

Strategy	Cost	Incremental cost	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER
LAIV	\$165.25	-	-8.4E-04	-	-
IIV	\$174.00	\$8.76	-9.2E-04	-8.0E-05	Dominated

LAIV, Live attenuated influenza vaccine; IIV, inactivated influenza vaccine; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio