

Supplementary Online Content

Prosser LA, Meltzer MI, Fiore A, Epperson S, Bridges CB, Hinrichsen V, Lieu TA. Effects of adverse events on the projected population benefits and cost-effectiveness of using live attenuated influenza vaccine in children aged 6 months to 4 years. *Arch Pediatr Adolesc Med*.

eAppendix

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eFigure 2. Sensitivity analysis for probability of hospitalization following vaccination with LAIV for lower-risk children aged 24-35 months compared to no vaccination.

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix.

Equation for calculating cost-effectiveness ratios.

$$\text{CE Ratio}_{\text{Age,Risk Status}} = \frac{\text{Total Costs with Vaccination}_{\text{Age,Risk Status}} - \text{Total Costs without Vaccination}_{\text{Age,Risk Status}}}{\text{Total QALYs with Vaccination}_{\text{Age,Risk Status}} - \text{Total QALYs without Vaccination}_{\text{Age,Risk Status}}}$$

Age = 6-11 months, 12-23 months, 3-4 years, 5-11 years, or 12-17 years

Risk Status = At high risk for influenza-related complications, or not

QALYs = Quality-adjusted life years

eTable 1. Expanded list of model inputs.^a

Variable	Most Likely Estimate	Range for Sensitivity Analysis	Source	Type of Distribution	Distribution Parameter 1	Distribution Parameter 2
Influenza illness attack rate (annual)			[1-10]			
6-23 months	0.157	0.02-0.35		Beta ^b	2.2	11.8
2 years	0.155	0.02-0.35		Derived ^c		
3-4 years	0.155	0.02-0.35		Derived ^c		
Probability of an outpatient visit for child with influenza illness ^{d,e}			[6, 11, 12]			
6-23 months	0.5	0.17-0.83		Beta	3.3	3.5
2 years	0.47	0.15-0.81		Beta	3.29	3.71
3-4 years	0.43	0.12-0.78		Beta	3.01	3.99
Probability of otitis media for a child with medically attended influenza illness			[13-16], expert panel			
6-23 months	0.63	0.33-0.8		Beta	6.3	3.7
2 years	0.58	0.27-0.8		Beta	5.22	3.78
3-4 years	0.39	0.17-0.6		Beta	6.24	9.76
Probability of non-hospitalized pneumonia or other outpatient complication for child with medically-attended influenza illness ^f			[11, 12], expert panel			
6-23 months	0.2	0.04-0.5		Beta	2.6	10.4
2 years	0.15	0.02-0.4		Beta	1.95	11.05
3-4 years	0.15	0.02-0.4		Beta	1.95	11.05
Hospitalizations for pneumonia or other respiratory conditions due to influenza per 10,000 lower-risk children ^g			[8, 11, 17, 18]			
6-23 months	28.3	1.9-80.0		Beta	5.5	244.5
2 years	17.1	0.5-56.8		Beta	3.4	246.6

^a Additional description of the structure and data inputs for the cost-effectiveness simulation model can be found in the following reference: Prosser LA, Bridges CB, Uyeki TM, et al. Health benefits, risks, and cost-effectiveness of influenza vaccination of children. *Emerg Infect Dis* 2006;12:1548-58.

^b Distributions for transition probabilities were assigned using most likely values and ranges identified in the literature and/or expert panel. For these parameters, primary data were not available and beta distributions were assigned to match the values identified in the table.

^c Distributions for age groups other than 6-23 months are based on the 6-23 month distribution multiplied by the ratio of the most likely estimates for the age group in question to 6-23 month olds (e.g., the distribution for 2 years is calculated by multiplying the distribution for 6-23 months by 0.155/0.157).

^d Estimates for healthy children shown in table. Probabilities are estimated to be twice as high for children at high risk for influenza-related complications.

^e Range for sensitivity analysis determined by expert opinion.

^f Estimates for healthy children shown in table. Probabilities are estimated to be up to five times as high for children at high risk for influenza-related complications. Base case estimates for high risk children are 1.6 times as high as for healthy children.

^g Higher-risk children are estimated to be hospitalized at 3-6 times the rate of healthy children.

Variable	Most Likely Estimate	Range for Sensitivity Analysis	Source	Type of Distribution	Distribution Parameter 1	Distribution Parameter 2
3-4 years	8.0	0-35.4		Beta	1.6	248.4
Probability of long-term sequelae following influenza-related hospitalization ^c	0.01	0.001-0.03	Expert panel	Beta ^h	1.3	11.7
Probability of death during influenza-related hospitalization	0.0009	0-0.002	[19] ^e	Beta ⁱ	1.7	18.3
Vaccine effectiveness in preventing influenza illness ^j						
IIV	0.69	0.4-0.9	[20] ^e	Beta	7.59	3.41
LAIV	0.838	0.6-0.96	[13] ^e	Beta	16.76	3.24
Probability of medically-attended vaccination-related adverse events						
Wheezing (LAIV only) ^k			[22-24]			
6-23 months, LR	0.0121	0.0077-0.0191		Beta	1486	18
2 years, LR	0.0037	0.0016-0.0100		Beta	1024	4
3-4 years, LR	0.0016	0.0004-0.0091		Beta	608	1
6-23 months, HR	0.0237	0.0137-0.0410		Beta	506	12
2 years, HR	0.0028	0.0007-0.0159		Beta	348	1
3-4 years, HR	0.0009	0.0002-0.0052		Beta	1061	1
Hospitalization for child with wheezing following vaccination ^l						
2-4 years	0.0423	0.0199-0.0891	[22-24]	Beta	142	6
Injection site reaction						
6-23 months	0.008	0.002-0.017	[7]	Beta	4.0	46.0
2 years	0.003			Derived ^m		
3-4 years	0.002			Derived ⁿ		
Systemic reaction (fever) ^o						
IIV						
6-23 months	0.013	0.001-0.025	[21]	Beta	5.2	194.8
2 years	0.011			Derived ^p		

^h Probability from distribution divided by 10.

ⁱ Probability from distribution divided by 100.

^j Assumes vaccine is poorly matched with circulating virus 1 in 10 years (i.e., vaccine effectiveness is assumed to be 0 in years with a poor match).

^k Parameter estimates and associated ranges were derived using data from the supplemental appendix to the clinical trial report by Belshe and colleagues (2007). Reference # 23 below.

^l This is the conditional probability of hospitalization for a child who has experienced a wheezing episode. The probability of hospitalization for a vaccinated child (i.e., the unconditional probability of hospitalization following vaccination with LAIV) can be calculated by multiplying the conditional probability of hospitalization given that a child has wheezing by the probability of wheezing for each age/risk group. For example for lower-risk 2 year olds, the unconditional probability of hospitalization is equal to $0.0037 * 0.0423 = 0.000157$.

^m Distributions for age groups other than 6-23 months are based on the 6-23 month distribution multiplied by the ratio of the most likely estimates for the age group in question to 6-23 month olds (e.g., the distribution for 2 years is calculated by multiplying the distribution for 6-23 months by $0.003/0.008$).

ⁿ Distributions for age groups other than 6-23 months are based on the 6-23 month distribution multiplied by the ratio of the most likely estimates for the age group in question to 6-23 month olds (e.g., the distribution for 2 years is calculated by multiplying the distribution for 6-23 months by $0.011/0.013$).

^o Definitions and follow-up for incidence of fever following vaccination vary by study. Rates are 2X higher for higher-risk subgroups.

^p Distributions for age groups other than 6-23 months are based on the 6-23 month distribution multiplied by the ratio of the most likely estimates for the age group in question to 6-23 month olds (e.g., the distribution for 2 years is calculated by multiplying the distribution for 6-23 months by $0.003/0.008$).

Variable	Most Likely Estimate	Range for Sensitivity Analysis	Source	Type of Distribution	Distribution Parameter 1	Distribution Parameter 2
3-4 years LAIV	0.009			Derived ^p		
6-23 months	0.035	0.003-0.068	[13,21,22]	Beta		
2 years	0.030			Derived ^q		
3-4 years	0.024			Derived ^q		
Anaphylaxis	0.00000025	0-0.000001	Expert panel	Beta ^f	0.5	19.5
Guillain Barré syndrome	0.000001	0-0.00001	Expert panel	Triangular	0.000001 (most likely)	0 (min), 0.000002 (max)
Influenza-related costs						
OTC medications ^s	\$3		[25-27], expert panel			
Physician visit for uncomplicated influenza ^t	\$32	\$10-98	Marketscan database ^u	Lognormal ^v	38	32
Physician visit for otitis media 6-23 months	\$88	\$26-223	Marketscan database ^w	Lognormal	111	88
2-4 years	\$94	\$26-226	Marketscan database ^w	Lognormal	113	94
Physician visit for non-hospitalized pneumonia 6-23 months	\$203	\$70-809	Marketscan database ^w	Lognormal	286	203
2-4 years	\$100	\$31-377	Marketscan database ^w	Lognormal	148	100
Hospitalization			[28]			
6-23 months, LR	\$6,300	5200-7400		Lognormal	6309	4685
2 years, LR	\$5,100	2500-12200		Lognormal	5077	4483
3-4 years, LR	\$5,500	2200-12400		Lognormal	5490	4541
6-23 months, HR	\$8,100	2100-22000		Lognormal	8141	5774
2 years, HR	\$7,500	2700-34400		Lognormal	7494	4827
3-4 years, HR	\$10,200	2700-34400		Lognormal	10182	6183
Long-term sequelae following influenza-related hospitalization ^x	\$707,000	\$0-1,132,000	[29]			

^q Distributions for age groups other than 6-23 months are based on the 6-23 month distribution multiplied by the ratio of the most likely estimates for the age group in question to 6-23 month olds (e.g., the distribution for 2 years is calculated by multiplying the distribution for 6-23 months by 0.030/0.035).

^f Probability from distribution divided by 100,000.

^s Vary by age, calculated by costing out recommended dose of acetaminophen for average weight in each age group.

^t Only a proportion of children with influenza illness are assumed to make a physician visit. ICD-9 codes: 487 and 487.0.

^u 1993-1997 Marketscan database, The Medstat Group, Ann Arbor, MI.

^v Lognormal distributions are approximated using the mean and median in Treeage. In this table, parameter 1 is the mean and parameter 2 is the median for each distribution.

^w 2001-2003 Marketscan database, The Medstat Group, Ann Arbor, MI.

^x Includes costs of lifetime care and special education.

Variable	Most Likely Estimate	Range for Sensitivity Analysis	Source	Type of Distribution	Distribution Parameter 1	Distribution Parameter 2
Vaccination costs						
Per dose, IIV ^y (children under 3)	\$13.52 ^z	1x-4x base case	[30]			
Per dose, IIV (children 3 and older)	\$14.32 ^z	1x-4x base case	[30]			
Per dose, LAIV ^y	\$17.90 ^{aa}		[30]			
Administration (0-2 visits) ^{bb}	\$28	\$11-45	[31]			
Parent time costs ^{cc}	\$36	\$0-72	[32, 33], expert panel			
Total vaccination costs, IIV						
6-23 months	\$97					
2 years	\$79	\$30-110				
3-4 years	\$73					
Total vaccination costs, LAIV						
6-23 months	\$105					
2 years	\$88					
3-4 years	\$80					
Vaccination-related adverse events						
Physician visit for injection site reaction ^{dd}	\$69	\$34-773	Marketscan database ^{ee}	Lognormal ^v	228	202
Anaphylaxis ^{ff}	\$3,054	\$59-15,564	Marketscan database ^{gg}	Lognormal ^v	5122	3054
Guillain Barré syndrome ^{hh}	\$26,433	\$7,540-89,297	Marketscan database ^{gg}	Lognormal ^v	36433	26433
Wheezing Episode ⁱⁱ	\$186	\$118-220	[37, 38], Expert panel			
Quality Adjustments ^{jj,kk} (Disutility associated with an event)						

^y Assumed 2 doses will be required for children under 5 receiving their first influenza vaccination.

^z Vaccine dose costs are based on 2006 CDC negotiated prices. Cost for children under 3 assumes thimerosal-free vaccine is used.

^{aa} Based on 2006 CDC negotiated price.

^{bb} CPT codes: 99211, 90471. Physician costs for vaccine administration at existing visit is \$11.30 (90471); \$22.60 for vaccine administration requiring a separate visit (99211).

^{cc} Each physician visit is assumed to take 2 hours of parent time valued at an average hourly wage rate of \$18.09. Parent time includes travel, waiting, and visit time. For vaccinations that do not require an extra visit, parent time includes only visit time specific to the vaccination.

^{dd} 5- minute visit, CPT code 99211

^{ee} 2001-2003 Marketscan database, The Medstat Group, Ann Arbor, MI.

^{ff} ICD-9 codes: 999.4, 995.0, 995.6x

^{gg} 2001-2003 Marketscan database, The Medstat Group, Ann Arbor, MI.

^{hh} ICD-9 code: 357.0

ⁱⁱ Costs of wheezing episode include cost of physician visit (CPT-4 code: 99213) or emergency department visit (CPT-4 code: 99283) and prescription medications (87% of children with wheezing episode will be prescribed a bronchodilator).

^{jj} Quality adjustments are included in the model as a one-time decrement in utility for each temporary health state. For example, an episode of influenza results in a one-time loss of 0.005 quality-adjusted life years [QALYs]. Utility losses were calculated by dividing the discounted time-traded off by the respondent's discounted life expectancy. Quality adjustments include health-related quality of life for child and parent as well as productivity losses for parents. Reference #39 below.

^{kk} Average life span used to calculate total QALYs lost due to life-long sequelae and death was 77.9-78.2 years depending on child's current age [Reference: NCHS United States Life Tables].

Variable	Most Likely Estimate	Range for Sensitivity Analysis	Source	Type of Distribution	Distribution Parameter 1	Distribution Parameter 2
Episode of influenza	0.005	0.002-0.009	[39]	Beta	7.35	1492.65
Otitis media	0.042	0.023-0.065	[40]	Beta	14.56	335.44
Non-hospitalized complications (pneumonia)	0.046	0.027-0.071	[40]	Beta	16.21	333.8
Hospitalization, pneumonia	0.076	0.054-0.100	[40]	Beta	37.85	462.15
Anaphylaxis	0.02	0.006-0.041	[39]	Beta	4.53	225.47
Guillain Barré syndrome	0.141	0.092-0.199	[39]	Beta	22.53	137.47
Wheezing episode	0.0018	0.0003 – 0.005	[41]	Beta	2.7	1497.3
Hospitalization following vaccination	0.076	0.054-0.100	[40]	Beta	37.85	462.15

eTable 2. Number of additional physician visits required to administer required doses, by age group.

	No extra visits required	One extra visit required	Two extra visits required
6-23 months	0.27	0.39	0.34
2 years	0.26	0.57	0.17
3-4 years	0.26	0.64	0.10

eTable 3. Cost-effectiveness ratios, compared to no vaccination, for use of inactivated and live attenuated influenza vaccination, mean (2.5% and 97.5% percentiles). CS = Cost Saving.

Age group, lower-risk	\$ per influenza episode averted ^a	
	Using inactivated influenza vaccine	Using live attenuated influenza vaccine
6-23 months	580 (CS; 6,020)	540 (CS; 5,500)
2 years	560 (20; 5,040)	500 (10; 4,480)
3-4 years	580 (130; 4,790)	510 (110; 4,150)

^a Numerator does not include productivity losses.

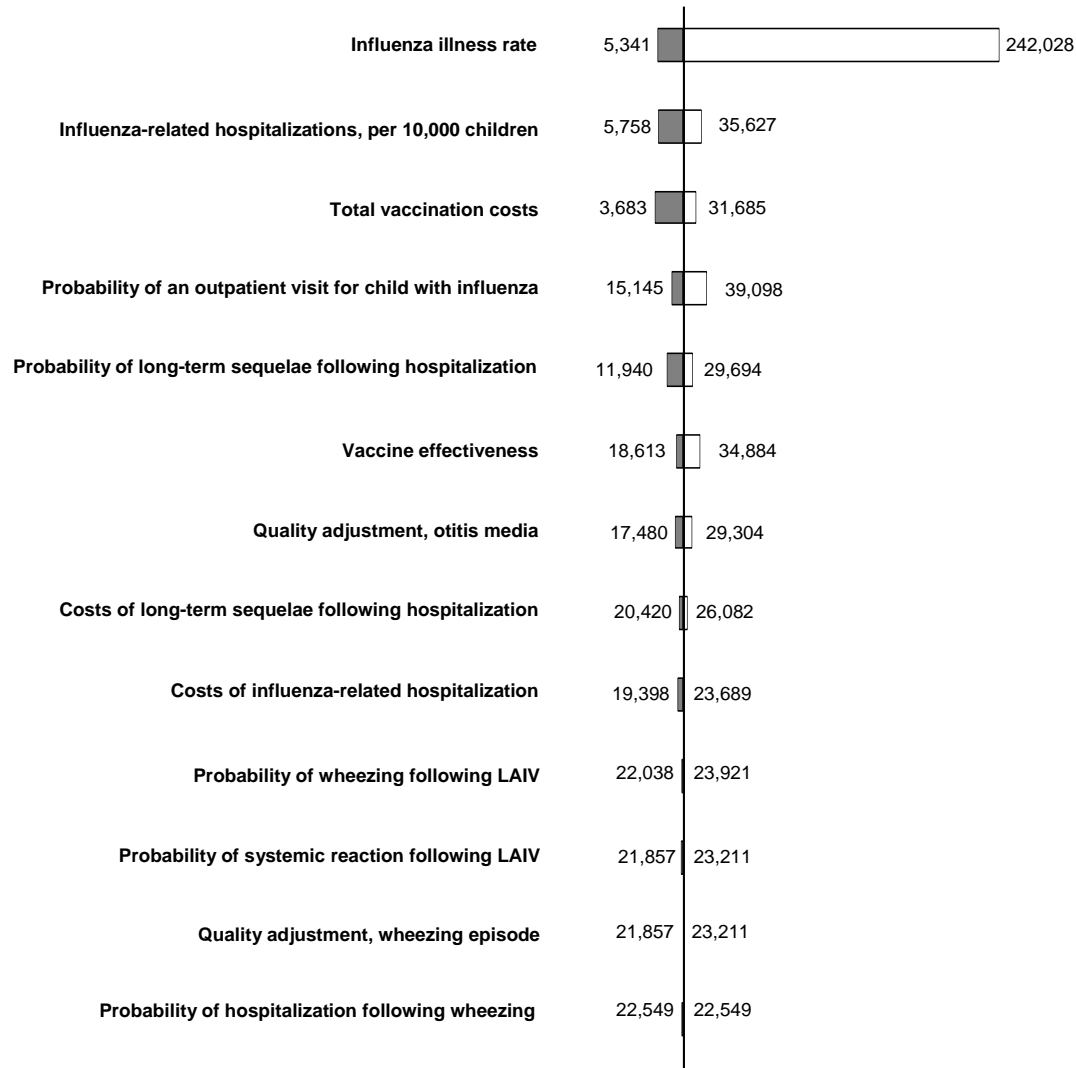
eTable 4. Sensitivity analysis for probability of hospitalization following vaccination with LAIV for lower-risk children aged 24-35 months compared to no vaccination.

Possible values for the probability of hospitalization following vaccination with LAIV	Incremental cost-effectiveness ratio (\$/QALY)
0.000	22,000
0.000157*	22,549
0.001	25,000
0.002	27,000
0.003	30,000
0.004	33,000
0.005	36,000
0.006	39,000
0.007	42,000**
0.008	46,000**
0.009	50,000**
0.010	54,000**
0.011	59,000**
0.012	64,000**
0.013	69,000**
0.014	74,000**
0.015	81,000**
0.016	87,000**
0.017	95,000**
0.018	103,000**
0.019	112,000**
0.020	122,000**

* Base case value for probability of hospitalization following vaccination with LAIV. Probability of hospitalization following wheezing for all vaccinated children (i.e., the unconditional probability of hospitalization following vaccination with LAIV) can be calculated by multiplying the probability of hospitalization for a child with wheezing by the probability of wheezing for each age/risk group. For example, for lower-risk 2 year olds, the unconditional probability of hospitalization is equal to 0.0037 * 0.0423 = 0.000157

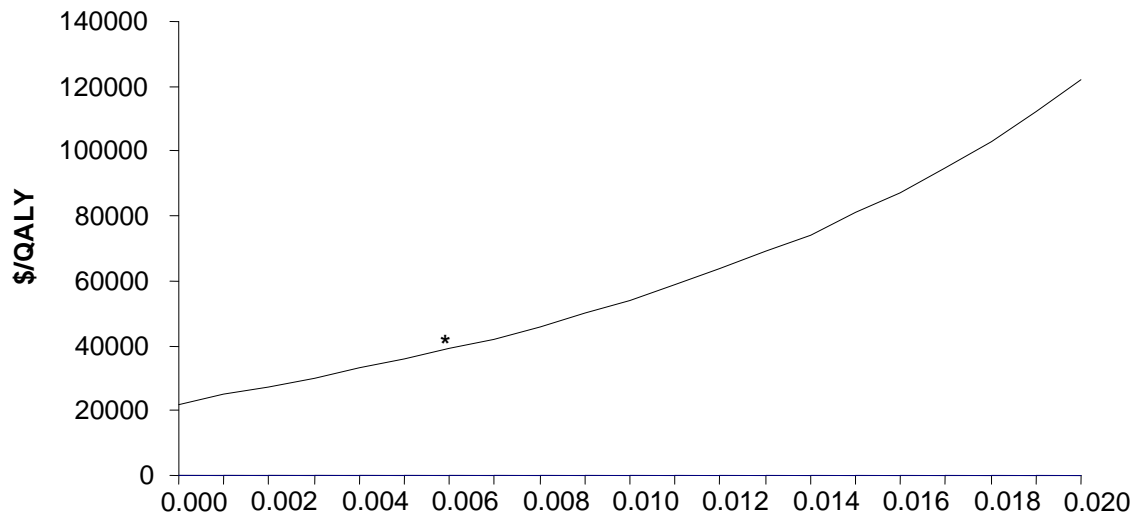
**Dominated by inactivated vaccine (LAIV is more costly and saves fewer QALYs).

eFigure 1. One-way sensitivity analyses on selected variables for lower-risk children aged 24-35 months, in \$/QALY.



Note: The Figure shows how the \$/QALY, for lower risk children aged 2 years, would change with a change in the values of a single input. For a given input, the values are changed using the range for that value as reported in eTable 1. This figure reports variables to which the results were most sensitive as well as all wheezing-related variables. Dark shading indicates change in cost-effectiveness ratios to ratios lower (i.e., more cost-effective) than base case; light shading indicates change in cost-effectiveness ratios to those higher (i.e., less favorable) than base case. Base case = \$22,549/QALY. Each parameter is varied over the range of plausible input values described in eTable 1.

eFigure 2. Sensitivity analysis for probability of hospitalization following vaccination with LAIV for lower-risk children aged 24-35 months compared to no vaccination.



Probability of All-Cause Hospitalization

*** Dominated by inactivated vaccine (LAIV is more costly yet saves QALYs).**

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