

# Economics of Influenza Vaccine Administration Timing for Children

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**T**he Advisory Committee on Immunization Practices (ACIP) has identified children as a high-risk group for influenza and recommends that children (aged 6 months to 18 years) receive influenza vaccine each year.<sup>1,2</sup> The 2009 influenza A(H1N1) (H1N1) pandemic highlights the importance of the timing of influenza vaccination as decision makers have endeavored to get vaccines to priority groups as soon as possible. While the presumption is that earlier vaccination is better so that a child is protected for a greater proportion of the influenza season, studies to date have not quantified how the economic value of vaccination may change with the timing of vaccine administration. Moreover, it is unclear how late in the influenza season vaccination still should be offered. Quantifying how the vaccine's economic value changes with the timing of vaccination may be important for vaccine production, distribution, and administration planning.

The 2009 H1N1 pandemic demonstrated the feasibility of manufacturing, delivering, and administering seasonal influenza vaccine by September or October.<sup>3</sup> Manufacturers and the supply chain were able to expeditiously produce and distribute seasonal influenza vaccine, despite manufacturing H1N1 influenza vaccine concurrently.<sup>4,6</sup> In fact, studies<sup>6,7</sup> have shown that in past years more than 70% of seasonal influenza vaccines have been available for administration by October. With evidence suggesting that earlier vaccination is possible, the next question is how much should be invested to ensure timely vaccination? The answer to this question depends in large part on the economic effect of delaying vaccination. Investment could occur all along the supply chain, from the very beginning (eg, investing to expand vaccine production capacity or to use antigen-sparing technology) to the very end (eg, investing to improve access to immunization clinics, school-based programs, health fairs, and healthcare provider visits). To address these issues, we constructed the following 2 sets of computer simulation models for children aged 2 to 18 years: (1) the children's influenza vaccination timing model, to quantify the incremental economic value of vaccinating a child earlier in the influenza season and the incremental cost of delaying vaccination, and (2) the children's monthly influenza vaccination decision model, to determine the cost-effectiveness of vaccinating versus not vaccinating a child for every month of the influenza season.

**Objectives:** To determine how much should be invested each year to encourage and operationalize the administration of influenza vaccine to children before November and how late the vaccine should be offered each year.

**Study Design:** Monte Carlo decision analytic computer simulation models.

**Methods:** The children's influenza vaccination timing model quantified the incremental economic value of vaccinating a child earlier in the influenza season and the incremental cost of delaying vaccination. The children's monthly influenza vaccination decision model evaluated the cost-effectiveness of vaccinating versus not vaccinating for every month of the influenza season.

**Results:** Getting children vaccinated by the end of October rather than when they are currently getting vaccinated could save society between \$6.4 million and \$9.2 million plus 653 and 926 quality-adjusted life-years (QALYs) and third-party payers between \$4.1 million and \$6.1 million plus 647 to 942 QALYs each year. Decision makers may want to continue offering influenza vaccination to children at least through the end of December. Vaccinating with trivalent inactivated virus vaccine was more cost-effective than vaccinating with live attenuated influenza vaccine for every month.

**Conclusion:** Policymakers could invest up to \$6 million to \$9 million a year to get children vaccinated in September or October without expending any net costs.

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## METHODS

We used TreeAge Pro 2009  
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see end of text.

**Take-Away Points**

The 2009 influenza A(H1N1) pandemic, as well as past influenza seasons, demonstrated the feasibility of administering seasonal influenza vaccine to children by September or October.

- Getting children vaccinated by the end of October rather than when they are currently getting vaccinated could save society between \$6.4 million and \$9.2 million plus 653 and 926 quality-adjusted life-years (QALYs) and third-party payers between \$4.1 million and \$6.1 million plus 647 to 942 QALYs each year.
- Trivalent inactivated virus vaccine (TIV) would be more cost-effective than live attenuated influenza vaccine (LAIV) for every month.
- Administration of TIV would remain cost-effective through December, and administration of LAIV would remain cost-effective through November.

the incremental cost-effectiveness of administering influenza vaccine to a child at different months of the influenza season (September to June) (Figure 1). Each vaccinated patient has a probability of experiencing local adverse effects (requiring 1 day of ibuprofen treatment) or systemic adverse effects (requiring 3 days of ibuprofen treatment). Vaccination confers immunity 2 weeks after administration. Vaccinated patients have a decreased probability of contracting influenza if exposed.

MA) to develop 2 models (the children’s influenza vaccination timing model and the children’s monthly influenza vaccination decision model) that each fed into a pediatric influenza outcomes subtree. The models depicted 1 full influenza season, with the baseline scenario assuming a societal perspective (accounting for direct and indirect illness costs), and an additional scenario assuming the third-party payer perspective (direct illness costs only). Details of the models are as follows.

Exposure to influenza is a function of the time left in the influenza season. Patients who contract influenza then proceed through the pediatric influenza outcomes subtree.

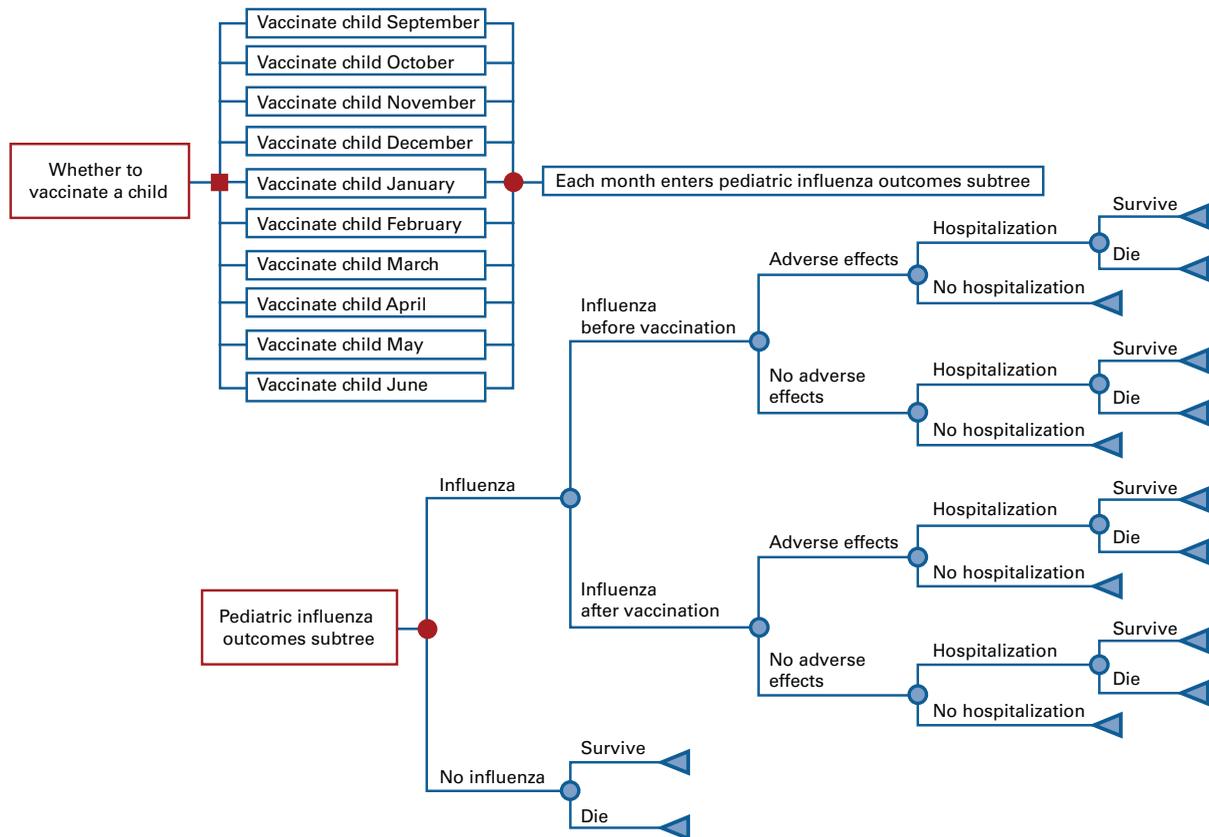
**Children’s Monthly Influenza Vaccination Decision Model**

The children’s monthly influenza vaccination decision model characterized the decision of whether to vaccinate a patient in a specific given month (Figure 2). For example, if a patient is seen in February, is it still cost-effective to vaccinate the patient? Separate models were created for each month of the year from September to June, encompassing the

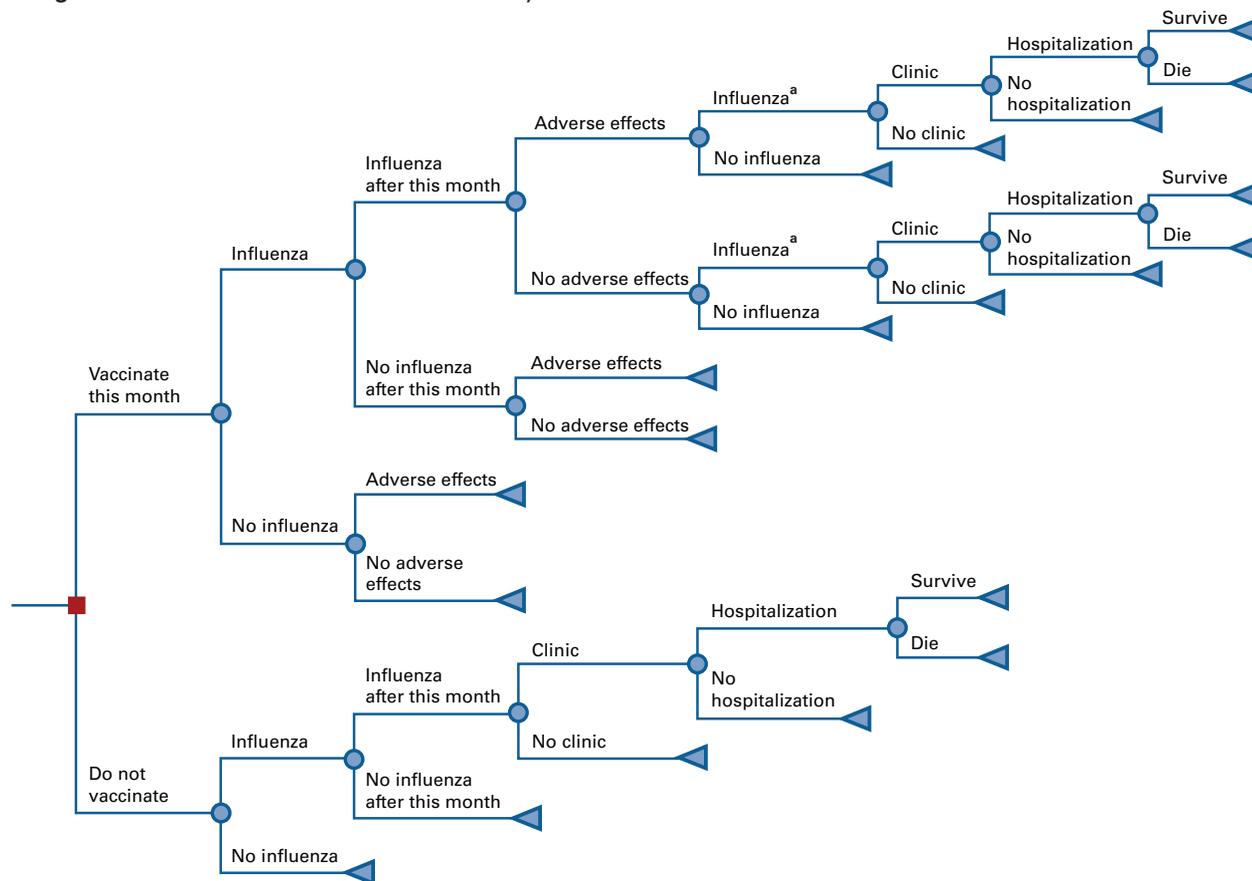
**Children’s Influenza Vaccination Timing Model**

The children’s influenza vaccination timing model Monte Carlo decision analytic computer simulation model determined

■ **Figure 1.** Structure of the Children’s Influenza Vaccination Timing Model



■ **Figure 2.** Structure of the Children’s Monthly Influenza Vaccination Decision Model



<sup>a</sup>Probability of influenza after vaccination, a function of vaccine efficacy and baseline risks of influenza.

influenza season. Similar to the children’s influenza vaccination timing model, patients who are vaccinated have chances of developing local or systemic adverse effects. Vaccination confers immunity after 2 weeks and reduces the probability of contracting influenza if exposed. Exposure to influenza is a function of the time left in the influenza season. Patients who contract influenza then proceed through the pediatric influenza outcomes subtree.

**Pediatric Influenza Outcomes Subtree**

For both sets of models, patients who develop influenza have probabilities of self-medicating with over-the-counter medications, visiting an outpatient clinic, or being hospitalized. Hospitalized patients have a probability of not surviving. Vaccination status affects these probabilities.

**Trivalent Inactivated (Killed) and Live Attenuated Influenza Virus Vaccines**

Different scenarios looked at trivalent inactivated virus vaccine (TIV) and live attenuated influenza vaccine (LAIV). This involved changing the costs and the efficacy

variable values to match each vaccine, as summarized in **Table 1.**

The following equation computed the incremental cost-effectiveness ratio (ICER) of vaccine administration in a given month versus another comparison month: (Cost of Vaccinating in Baseline Month – Cost of Vaccinating in Comparison Month)/(Effectiveness of Vaccinating in Baseline Month – Effectiveness of Vaccinating in Comparison Month).

To assess if vaccinating is cost-effective, the threshold used in our model was \$50,000/quality-adjusted life-year (QALY), which is a frequently cited criterion for cost-effectiveness analysis in the United States.<sup>21</sup> Based on nonparametric estimates by Shiroiwa et al,<sup>22</sup> this US cost-effectiveness threshold was similar to previously reported thresholds.

**National Investment Using the Children’s Influenza Vaccination Timing Model**

Using the children’s influenza vaccination timing model, we then constructed a model to project the potential eco-

■ **Table 1.** Data Inputs for Model Variables

Variable	Mean (Range)	Source
<b>Costs, \$</b>		
TIV	15.00	Thomson Healthcare, <sup>8</sup> 2008
LAIV	25.00	Thomson Healthcare, <sup>8</sup> 2008
<b>Influenza treatment</b>		
Over-the-counter medications	15.61 (11.70-19.51)	Thomson Healthcare, <sup>8</sup> 2008
Outpatient visit	51.00	Jordan et al, <sup>9</sup> 2006
Productivity loss for outpatient visit	64.08 (50.04-9.12)	US Bureau of Labor Statistics, <sup>10</sup> 2007
Hospitalization age group, y		
<2	2538 (2323-2753)	Levit et al, <sup>11</sup> 2008
2-4	2512 (2012-3012)	Levit et al, <sup>11</sup> 2008
5-9	2421 (1877-2965)	Levit et al, <sup>11</sup> 2008
10-14	2829 (1634-4024)	Levit et al, <sup>11</sup> 2008
15-18	2988 (2196-3780)	Levit et al, <sup>11</sup> 2008
Death in hospital	5000	Smith and Roberts, <sup>12</sup> 2002
Treatment of vaccine adverse effects	0.76 (0.68-3.82)	Thomson Healthcare, <sup>8</sup> 2008
<b>Durations</b>		
Influenza, d	7	Smith and Roberts, <sup>12</sup> 2002; Rothberg et al, <sup>13</sup> 2003; Rothberg and Rose, <sup>14</sup> 2005
Clinic visit, h	4	Smith and Roberts, <sup>12</sup> 2002; Rothberg et al, <sup>13</sup> 2003; Rothberg and Rose, <sup>14</sup> 2005
<b>Utility decrements, QALYs</b>		
Influenza without hospitalization	0.65 (0.49-0.81)	Tengs and Wallace, <sup>15</sup> 2000; Sackett and Torrance, <sup>16</sup> 1978
Influenza with hospitalization	0.50 (0.38-0.63)	Tengs and Wallace, <sup>15</sup> 2000; Sackett and Torrance, <sup>16</sup> 1978
Vaccine adverse effects	0.95 (0.71-1.00)	Tengs and Wallace, <sup>15</sup> 2000
<b>Probabilities</b>		
<b>Clinical outcomes without vaccination</b>		
Influenza throughout the year	0.125 (0.05-0.20)	Rivetti et al, <sup>17</sup> 2006
Clinic visit given influenza vaccination, age group, y		
<2, 2-4	0.455 (0.357-0.553)	Molinari et al, <sup>18</sup> 2007
5-9, 10-14, 15-18	0.318 (0.257-0.379)	Molinari et al, <sup>18</sup> 2007
Hospitalization given influenza vaccination, age group, y		
<2, 2-4	0.0141 (0.0094-0.0188)	Molinari et al, <sup>18</sup> 2007
5-9, 10-14, 15-18	0.0006 (0.0004-0.0008)	Molinari et al, <sup>18</sup> 2007
<b>Mortality given no influenza vaccination, age group, y</b>		
<2, 2-4	0.00004 (0.00003-0.00005)	Molinari et al, <sup>18</sup> 2007
5-9, 10-14, 15-18	0.00001	Molinari et al, <sup>18</sup> 2007
<b>Vaccine</b>		
Adverse effects	0.03	Belshe et al, <sup>19</sup> 2007
TIV	0.41 (0.29-0.59)	Jefferson et al, <sup>20</sup> 2008
LAIV	0.18 (0.11-0.29)	Jefferson et al, <sup>20</sup> 2008
Reduction in hospitalization	0.5	Jefferson et al, <sup>20</sup> 2008
Reduction in mortality	0.5	Jefferson et al, <sup>20</sup> 2008

LAIV indicates live attenuated influenza vaccine; QALYs, quality-adjusted life-years; TIV, trivalent inactivated virus vaccine.

conomic value (from the societal and third-party payer perspectives) of moving the current timing of pediatric vaccination to October throughout the United States. The US Census data (<http://www.census.gov/>) from 2008 provided the sizes of the different age groups as follows: 2 to 4 years (21,005,852 children), 5 to 9 years (20,065,249 children), 10 to 14 years (20,054,627 children), and 15 to 18 years (21,514,358 children). Vaccination coverage among children was obtained from previous studies<sup>23,24</sup> by the Centers for Disease Control and Prevention (CDC).

### Data Inputs

Table 1 lists the models' data inputs, their respective distributions, and their sources. The cost of vaccine was the average wholesale price of TIV and LAIV, respectively.<sup>8</sup> The cost of over-the-counter medications comprised the average wholesale price of acetaminophen (triangular distribution).<sup>8</sup> The cost of hospitalization for influenza was obtained from the National Inpatient Survey of the Healthcare Cost and Utilization Project (HCUP).<sup>9</sup> The cost of death was derived from differences in invasive pneumococcal disease costs in adults discharged alive versus those not surviving, which varied from \$3700 to \$14,000 based on HCUP data.<sup>10,25</sup> The cost of an outpatient visit was obtained from a systemic review article<sup>11</sup> regarding the effectiveness of vaccinating healthy children. The cost of vaccine adverse effects consisted of the average wholesale price of ibuprofen, assuming 1 to 3 days of ibuprofen treatment.<sup>8</sup> Productivity losses from an outpatient visit comprised 4 hours of lost median wages (incurred by a parent missing 4 hours of work to bring a child to the clinic).<sup>12</sup>

Durations of clinic visits (in hours) and influenza (in days) were obtained from previous studies.<sup>10,13,14</sup> Cochrane<sup>15,16</sup> systematic reviews provided probabilities of influenza and vaccine efficacy (in preventing influenza, hospitalization, and death). Probabilities of various influenza outcomes were obtained from a CDC study.<sup>17</sup> Probabilities of vaccine adverse effects were obtained from a 2007 study.<sup>18</sup>

All utility variables drew from triangular distributions and are expressed in QALYs; all other variables drew from normal and beta distributions.<sup>19,20,26</sup> When possible, data inputs were obtained from published meta-analyses. The CDC<sup>27</sup> monthly influenza surveillance data from 2000 to 2008 were used to generate the distribution of monthly influenza risk. Each simulation run randomly drew from 1 of 9 influenza seasons from 2000 to 2008.

A 3% discount rate converted costs and effectiveness measures into 2009 values. Effectiveness was expressed in QALYs. Each patient who experienced neither vaccine adverse effects nor influenza accrued 1.00 QALY.<sup>26</sup> The occurrence of vaccine adverse effects, influenza, or hospitalization each caused rela-

tive QALY reductions.<sup>19,20</sup> Death resulted in a QALY loss based on the QALY-adjusted life expectancy of that patient's age.<sup>28</sup>

### Sensitivity Analysis

Sensitivity analyses varied variable values across the ranges listed in Table 1. We also looked specifically at how the age of the vaccine recipient (2-18 years) affected our results. This involved cohorts of the following age groups: 2 to 4, 5 to 9, 10 to 14, and 15 to 18 years. In addition, specific scenarios examined how much could be invested per child to encourage earlier vaccination with vaccination still remaining cost-effective. Probabilistic (Monte Carlo) sensitivity analyses examined the effects of varying all variables simultaneously using all distributions in Table 1.

## RESULTS

### Children's Influenza Vaccination Timing Model

Each simulation run comprised sending 5000 simulated patients 1000 times through the model, for a total of 5 million trials. Simulations found September and October to be the optimal months for vaccination, dominating other months (ie, yielding lower costs and greater effectiveness than other months).

For TIV, delaying vaccination until November cost society an additional \$0.13 to \$0.26 and 0.000016 to 0.000018 QALY per patient and cost third-party payers an additional \$0.08 to \$0.16 and up to 0.000017 QALY per patient. For LAIV, delays were even more costly for society (an additional \$0.18-\$0.37 and 0.000024-0.000025 QALY per patient) and for third-party payers (an additional \$0.10-\$0.27 and 0.000024-0.000026 QALY per patient).

Various scenarios explored the effects of investing different amounts of money per child to facilitate October vaccination. For TIV, October vaccination remained cost-effective up to and including a \$0.75 per child investment (the ICER from the societal perspective ranged from \$27,901-\$36,413 per QALY and from the third-party payer perspective ranged from \$33,191-\$39,490 per QALY). For LAIV, October vaccination remained cost-effective up to and including a \$1.25 per child investment (the ICER from the societal perspective ranged from \$36,538-\$46,266 per QALY and from the third-party payer perspective ranged from \$41,431-\$48,282 per QALY). This reinforced that delaying vaccination for LAIV was worse than delaying vaccination for TIV.

### National Investment Using the Children's Influenza Vaccination Timing Model

Table 2 and Table 3 summarize the national investment results from the societal and third-party payer perspectives,

■ **Table 2.** US Potential Savings of Moving Pediatric Influenza Vaccinations (TIV and LAIV) Before November From the Societal Perspective

Age Group, y <sup>a</sup>	No. Currently Vaccinated, millions	Potential Savings From Moving 1000 Vaccinations to Before November		Potential Savings From Moving All Vaccinations to Before November	
		Costs, \$	QALYs	Costs, \$, millions	QALYs
<b>November</b>					
2-4	2.27	261-371	0.02-0.03	0.59-0.84	39-57
5-9	1.41	134-183	0.02-0.03	0.19-0.26	24-35
10-14	1.41	132-178	0.02-0.02	0.19-0.25	25-34
15-18	1.51	126-193	0.02-0.02	0.19-0.29	24-36
<b>December</b>					
2-4	0.92	656-943	0.05-0.07	0.60-0.87	42-61
5-9	0.57	351-494	0.05-0.07	0.20-0.28	27-38
10-14	0.57	345-474	0.05-0.06	0.20-0.27	26-37
15-18	0.62	347-504	0.04-0.07	0.21-0.31	27-41
<b>January</b>					
2-4	0.47	1854-2662	0.14-0.18	0.87-1.25	66-86
5-9	0.30	983-1406	0.13-0.19	0.29-0.41	39-55
10-14	0.30	966-1335	0.13-0.18	0.28-0.39	38-53
15-18	0.31	963-1425	0.13-0.19	0.30-0.45	39-58
<b>February</b>					
2-4	0.25	2939-4229	0.22-0.29	0.74-1.07	54-73
5-9	0.16	1532-2184	0.21-0.29	0.24-0.34	32-46
10-14	0.16	1519-2105	0.21-0.29	0.24-0.33	32-45
15-18	0.17	1530-2220	0.20-0.29	0.26-0.37	33-49
<b>March</b>					
2-4	0.08	5123-7258	0.36-0.50	0.43-0.61	31-42
5-9	0.05	2634-3694	0.35-0.50	0.14-0.19	18-26
10-14	0.05	2589-3632	0.35-0.49	0.14-0.19	18-26
15-18	0.06	2625-3758	0.35-0.49	0.15-0.21	19-28
<b>Total</b>	—	—	—	<b>6.44-9.19</b>	<b>653-926</b>

LAIV indicates live attenuated influenza vaccine; QALYs, quality-adjusted life-years; TIV, trivalent inactivated virus vaccine.

<sup>a</sup>Percentages of vaccine coverage are 32.0% (2-4 years), 20.8% (5-9 years), 20.8% (10-14 years), and 20.8% (15-18 years), from the Centers for Disease Control and Prevention.<sup>23</sup>

respectively. The tables give the number of children who are currently being vaccinated in each month after October and then the potential value of moving all these vaccinations to before November. As summarized in Table 2, the potential total savings is between \$6.4 million and \$9.2 million from the societal perspective, suggesting that society could invest this much money into vaccinating children before November. In addition, this could save between 653 and 926 QALYs. As summarized in Table 3, the potential total savings for third-party payers is between \$4.1 million and \$6.1 million, with an accompanying 647 to 942 QALYs saved.

### Children’s Monthly Influenza Vaccination Decision Model

Each simulation run comprised sending 1000 simulated patients 1000 times through the model, for a total of 1 million trials. Table 4 summarizes the results from these simulation runs for each month. Using the \$50,000 per QALY threshold, TIV remained cost-effective through December for society (\$33,639-\$44,511 per QALY) and for third-party payers (\$32,823-\$48,847 per QALY). After December, the ICER of vaccination exceeded \$50,000 per QALY (the shaded area in Table 4). Results changed with LAIV. Vac-

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**Table 3.** US Potential Savings of Moving Pediatric Influenza Vaccinations (TIV and LAIV) Before November From the Third-Party Payer Perspective

Age Group, y <sup>a</sup>	No. Currently Vaccinated, millions	Potential Savings From Moving 1000 Vaccinations to Before November		Potential Savings From Moving All Vaccinations to Before November	
		Costs, \$	QALYs	Costs, \$, millions	QALYs
<b>November</b>					
2-4	2.27	164-272	0.02-0.03	0.37-0.62	39-59
5-9	1.41	75-101	0.02-0.02	0.11-0.14	24-34
10-14	1.41	77-104	0.02-0.02	0.11-0.15	24-34
15-18	1.51	77-111	0.02-0.03	0.12-0.17	26-38
<b>December</b>					
2-4	0.92	448-729	0.05-0.07	0.41-0.67	43-62
5-9	0.57	204-281	0.05-0.07	0.12-0.16	26-37
10-14	0.57	195-278	0.05-0.07	0.11-0.16	26-37
15-18	0.62	212-303	0.05-0.07	0.13-0.19	28-41
<b>January</b>					
2-4	0.47	1281-1930	0.13-0.20	0.60-0.91	60-94
5-9	0.30	589-810	0.13-0.18	0.17-0.24	39-54
10-14	0.30	564-791	0.13-0.18	0.16-0.23	38-54
15-18	0.31	591-845	0.13-0.19	0.86-0.26	41-59
<b>February</b>					
2-4	0.25	2029-3032	0.20-0.31	0.51-0.76	51-77
5-9	0.16	923-1284	0.21-0.29	0.14-0.20	32-45
10-14	0.16	884-1245	0.21-0.29	0.14-0.19	32-45
15-18	0.17	926-1320	0.20-0.29	0.16-0.22	34-49
<b>March</b>					
2-4	0.08	3536-5170	0.35-0.51	0.30-0.43	29-43
5-9	0.05	1571-2196	0.35-0.50	0.08-0.11	18-26
10-14	0.05	1499-2124	0.35-0.50	0.08-0.11	18-26
15-18	0.06	1581-2269	0.35-0.50	0.09-0.13	19-28
<b>Total</b>	—	—	—	<b>4.10-6.06</b>	<b>647-942</b>

LAIV indicates live attenuated influenza vaccine; QALYs, quality-adjusted life-years; TIV, trivalent inactivated virus vaccine.

<sup>a</sup>Percentages of vaccine coverage are 32.0% (2-4 years), 20.8% (5-9 years), 20.8% (10-14 years), and 20.8% (15-18 years), from the Centers for Disease Control and Prevention.<sup>23</sup>

cinating patients with LAIV remained cost-effective only through November for society (\$28,988-\$38,350 per QALY) and for third-party payers (\$33,497-\$41,038 per QALY). The ICER for LAIV vaccination quickly exceeds \$50,000 per QALY in December and onward. By March, no vaccination dominates vaccination for TIV and for LAIV. In other words, vaccination not only costs more but also resulted in decreased effectiveness.

For every month, TIV is more cost-effective than LAIV. For example, in October from the societal perspective, TIV's ICER ranged from \$21,005 to \$29,355 per QALY, while

LAIV's ICER ranged from \$27,055 to \$34,074 per QALY (Table 4). From the third-party payer perspective, this trend held as well: TIV's ICER in October ranged from \$26,507 to \$32,327 per QALY, while LAIV's ICER ranged from \$31,387 to \$38,337 per QALY.

## DISCUSSION

### Advantages of Earlier Vaccination

Our results demonstrate how the economic value of influenza vaccine for children can vary substantially with the

■ **Table 4.** Incremental Cost-Effectiveness Ratio of Vaccination (vs No Vaccination) for Each Month

Month	\$ per QALY			
	Societal Perspective		Third-Party Payer Perspective	
	Low	High	Low	High
<b>TIV</b>				
October	21,005	29,355	26,507	32,327
November	23,420	32,501	29,426	36,407
December	33,639	44,511	32,823	48,847
January	51,827	63,021	56,788	65,830
February	101,210	241,278	211,081	230,652
March	Dominated <sup>a</sup>	Dominated <sup>a</sup>	Dominated <sup>a</sup>	Dominated <sup>a</sup>
<b>LAIV</b>				
October	27,055	34,074	31,387	38,337
November	28,988	38,350	33,497	41,038
December	41,403	50,530	45,028	56,917
January	60,241	68,879	62,677	74,426
February	188,774	204,919	194,205	231,406
March	Dominated <sup>a</sup>	Dominated <sup>a</sup>	Dominated <sup>a</sup>	Dominated <sup>a</sup>

LAIV indicates live attenuated influenza vaccine; QALY, quality-adjusted life-year; TIV, trivalent inactivated virus vaccine.  
<sup>a</sup>“Vaccinate March” is dominated by “do not vaccinate.”

timing of vaccine administration and can rapidly decay with delays in vaccination. Earlier vaccination has the following potential advantages:

**Preventing November and December Cases.** A substantial number of influenza cases occur in November and December and can only be prevented if influenza vaccine is administered at least 2 weeks before this time (because influenza vaccine typically takes 2 weeks to achieve seroprotection).

**Protecting Against Early Peaking Influenza Seasons.** Some influenza seasons over the past decade have arrived earlier than usual. This makes earlier protection even more valuable.

**Achieving Early Local Herd Immunity.** Our study may in some ways underestimate the value of earlier vaccination because it could achieve earlier local herd immunity and reduce local influenza risk, as suggested by findings of previous studies.<sup>29</sup> In other words, immunizing a large proportion of children in a school before influenza enters the population may impede the spread of influenza and confer protection to unvaccinated children. Our model did not explicitly model herd immunity because effects may vary significantly among populations.

**Decreasing Inventory Holding Costs.** Another potential benefit of earlier vaccination is decreasing the length of time different locations (including clinics) must store influenza vaccine. Inventory costs are not insignificant, especially in places with limited refrigerator space, and they vary significantly among locations.

Therefore, while efforts have focused on increasing vaccine coverage among children, focusing on earlier vaccination may be worthwhile as well. Although some recent studies<sup>30-32</sup> have focused on the importance of administering vaccine early during a pandemic, the literature to date is sparse on the issue of seasonal influenza vaccine timing. A study<sup>33</sup> in Israel demonstrated that the effectiveness of influenza vaccine decreases with later administration during the influenza season. A multistate case-cohort study<sup>34</sup> examined but did not focus on pediatric vaccination timing. The ACIP<sup>1,2</sup> has advocated influenza vaccination in October or November. However, little is known about whether parents understand the effect of seasonal influenza vaccination timing or the extent to which clinics, local health departments, workplaces, and other vaccination locations are encouraging earlier vaccination.

Evidence suggests that earlier vaccination is feasible and would not result in decreased vaccine efficacy.<sup>35,36</sup> Manufacturing, supply chain, and vaccine administration capacity did not prevent the expeditious rollout of seasonal influenza vaccine in August and September 2009. In addition, strain selection typically occurs in January or February before the influenza season, leaving more than the typical 4 to 6 months required for traditional egg-based vaccine production, which suggests that promoting October vaccination will not adversely affect vaccine efficacy.<sup>35,36</sup> The fact that historically more than 70% of seasonal influenza vaccines are available to

be administered by October but more than 50% of children are vaccinated after October implies that the vaccination delays have not been due to inherent production timeline constraints.<sup>37</sup> In other words, promoting earlier vaccination may not require earlier development or substantially strain distribution systems.

Decision makers (eg, policymakers, manufacturers, distributors, third-party payers, administrators, clinicians, and school officials) can take various steps to get vaccines to children earlier. They can increase access (eg, making hours and locations more convenient) to vaccination locations (eg, clinics or alternative locations), order vaccines further in advance, and initiate vaccination campaigns sooner. Educational and awareness programs may convince parents to bring their children to vaccination locations more promptly. Parents and schools may be important targets. Parental availability can affect when their children are vaccinated. Working parents may struggle to find time to bring their children to physician offices. School-based vaccination campaigns could help vaccinate children who would otherwise wait until their next scheduled physician visits.

Investment can come in many forms such as supporting facilities and personnel to expand vaccination availability during off-hours and weekends, increasing refrigerator capacity, and conducting educational campaigns. Another possibility is financial incentives to patients or physicians to vaccinate earlier. However, results of prior studies<sup>38-40</sup> have been equivocal about the potential effectiveness of such incentives.

Making such operational changes to ensure timely vaccination may require some investment.<sup>41-43</sup> Our results suggest that October remains cost-effective even when investing up to \$0.75 to \$1.25 per child. In other words, there may be some room for investment to ensure that children are vaccinated earlier. Decision makers may consider committing resources to enhance vaccine production, shipping, and distribution. Other possibilities are increasing the number of vaccination locations (eg, schools or health fairs) and the hours of availability. They also may want to include the timing concept in vaccine education and awareness campaigns. Another possibility is direct financial incentives to parents who normally would not get their children vaccinated in a timely manner.

While the effect of vaccination timing holds for TIV and LAIV, TIV is more cost-effective than LAIV for every given month (ie, LAIV's potential efficacy advantages do not outweigh its higher cost).<sup>44-47</sup> As an intranasal formulation that does not require needles, LAIV has potential administration advantages that are hard to capture in economic models. However, the higher cost of LAIV has hindered its adoption and continues to make TIV the more cost-effective choice for children when both are available.

Advocating earlier vaccination in no way suggests that vaccination should not be continuously offered for a large portion of the influenza season. The savings presented herein are only from getting children vaccinated earlier and not from shutting down vaccination operations and capabilities after October. In fact, results from the children's monthly influenza vaccination decision model suggest that influenza vaccination remains cost-effective through the end of December. This may help decision makers (eg, clinicians, policymakers, healthcare administrators, vaccine logicians, vaccine purchasers) justify maintaining influenza vaccination operations (eg, maintaining refrigerator space for vaccines, retaining staff to administer vaccines, ordering vaccines, offering vaccine to patients) at least into January. Clinicians must know what to do when parents and children may arrive at vaccination locations late in the influenza season. Monthly results in Table 4 also suggest differences in the cost-effectiveness of TIV and LAIV: TIV vaccination remains cost-effective through the end of December, but LAIV remains cost-effective only through the end of November.

### Limitations

Models by definition are simplifications of clinical and public health situations and decision making and cannot completely represent every possible influenza and vaccination event and outcome. Models also cannot fully incorporate the sociodemographic and clinical diversity of the pediatric population. Comorbidities may alter the benefits of influenza vaccination. Moreover, our model did not account for the potential effects of vaccination on influenza transmission (eg, earlier vaccination generating herd immunity sooner and conferring greater protection to the entire population).

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## CONCLUSIONS

Quantifying how the economic value of vaccinating children may change with the timing of vaccine administration may help decision makers understand how early and late the vaccine should be available and how much to invest to get children vaccinated earlier. Our study found that policymakers could invest up to \$6 million to \$9 million a year to get children vaccinated in September or October without expending any net costs. For every month, TIV was more cost-effective than LAIV. Administration of TIV remained cost-effective through December, and administration of LAIV remained cost-effective through November. Clinicians, policymakers, manufacturers, administrators, school officials, and other decision makers should consider strategies, programs, policies, and practices that will ensure children are vaccinated earlier.

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## REFERENCES

- Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA: Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2002;51(RR-3):1-31.
- Fiore AE, Shay DK, Broder K, et al; Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep.* 2008;57(RR-7):1-60.
- Flu Supply News. October update on seasonal flu vaccine availability: 2009 seasonal influenza vaccination. October 14, 2009. <http://www.flusupplynews.com/documents/CDCUpdateonSeasonalFluVaccineAvailability10-14-09.pdf>. Accessed January 2, 2010.
- Seasonal trivalent influenza vaccine for 2009-2010. *Med Lett Drugs Ther.* 2009;51(1321):73-74.
- Michigan Department of Community Health. Preparations for seasonal influenza and 2009 H1N1 influenza. *Mich Med.* 2009;108(4):18-19.
- Layton C, Lenfestey N. *Influenza Vaccine Manufacturing: Issue Brief: October 2005*. Research Triangle Park, NC: RTI International; 2005.
- Wallace GS. Vaccine supply update & programmatic implications. Paper presented at: Advisory Committee on Immunization Practices; February 27, 2008; Atlanta, GA.
- Thomson Healthcare. *Red Book 2007: Pharmacy's Fundamental Reference*. Montvale, NJ: Thomson Reuters; 2007.
- Jordan R, Connock M, Albon E, et al. Universal vaccination of children against influenza: are there indirect benefits to the community? a systematic review of the evidence. *Vaccine.* 2006;24(8):1047-1062.
- US Bureau of Labor Statistics. *National Compensation Survey: Occupational Wages in the United States, June 2006*. Washington, DC: US Dept of Labor; 2007.
- Levit K, Stranges E, Ryan K, Elixhauser A. *HCUP Facts and Figures, 2006: Statistics on Hospital-Based Care in the United States*. Rockville, MD: Agency for Healthcare Research and Quality; 2008. <http://www.hcup-us.ahrq.gov/reports.jsp>. Accessed January 2, 2010.
- Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med.* 2002;113(4):300-307.
- Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. *Ann Intern Med.* 2003;139(5, pt 1):321-329.
- Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. *Am J Med.* 2005;118(1):68-77.
- Tengs TO, Wallace A. One thousand health-related quality-of-life-estimates. *Med Care.* 2000;38(6):583-637.
- Sackett DL, Torrance GW. The utility of different health states as perceived by the general public. *J Chronic Dis.* 1978;31(11):697-704.
- Rivetti D, Jefferson T, Thomas R, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev.* 2006;3:CD004876.
- Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine.* 2007;25(27):5086-5096.
- Belshe RB, Edwards KM, Vesikari T, et al; CAIV-T Comparative Efficacy Study Group. Live attenuated versus inactivated influenza vaccine in infants and young children [published correction appears in *N Engl J Med.* 2007;356(12):1283]. *N Engl J Med.* 2007;356(7):685-696.
- Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev.* 2008;2:CD004879.
- Bell CM, Urbach DR, Ray JG, et al. Bias in published cost effectiveness studies: systematic review. *BMJ.* 2006;332(7543):699-703.
- Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ.* 2009.
- Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6 months-18 years: eight immunization information system sentinel sites, United States, 2008-09 influenza season. *MMWR Morb Mortal Wkly Rep.* 2009;58(38):1059-1062.
- Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children and adults: United States, 2008-09 influenza season. *MMWR Morb Mortal Wkly Rep.* 2009;58(39):1091-1095.
- Smith KJ, Zimmerman RK, Lin CJ, et al. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. *Vaccine.* 2008;26(11):1420-1431.
- Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using measures to create condition-specific values. *Med Care.* 1998;36(6):778-792.
- Centers for Disease Control and Prevention (CDC). Flu activity & surveillance. 2009. <http://www.cdc.gov/flu/weekly/fluactivity.htm>. Accessed January 2, 2010.
- Wilmoth JR, Shkolnikov V. Human Mortality Database. 2008. <http://www.mortality.org/>. Accessed January 2, 2010.
- Medlock J, Galvani AP. Optimal influenza vaccine distribution. *Science.* 2009;325(5948):1705-1708.
- Mylius SD, Hagenaars TJ, Lugner AK, Wallinga J. Optimal allocation of pandemic influenza vaccine depends on age, risk and timing. *Vaccine.* 2008;26(29-30):3742-3749.
- Germann TC, Kadau K, Longini IM Jr, Macken CA. Mitigation strategies for pandemic influenza in the United States. *Proc Natl Acad Sci U S A.* 2006;103(15):5935-5940.
- Yang Y, Sugimoto JD, Halloran ME, et al. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science.* 2009;326(5953):729-733.
- Chodick G, Heymann AD, Green MS, Kokia E, Shalev V. Late influenza vaccination is associated with reduced effectiveness. *Prev Med.* 2006;43(1):71-76.
- Szilagyi PG, Fairbrother G, Griffin MR, et al; New Vaccine Surveillance Network. Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. *Arch Pediatr Adolesc Med.* 2008;162(10):943-951.
- Russell CA, Jones TC, Barr IG, et al. Influenza vaccine strain selection and recent studies on the global migration of seasonal influenza viruses. *Vaccine.* 2008;26(suppl 4):D31-D34.
- Hehme N, Colegate T, Palache B, Hessel L. Influenza vaccine supply: building long-term sustainability. *Vaccine.* 2008;26(suppl 4):D23-D26.
- Tan L; American Medical Association. Strengthening the supply of routinely recommended vaccines in the United States: a perspective from the American Medical Association. *Clin Infect Dis.* 2006;42(suppl 3):S121-S124.
- Fairbrother G, Hanson KL, Friedman S, Butts GC. The impact of physician bonuses, enhanced fees, and feedback on childhood immunization coverage rates. *Am J Public Health.* 1999;89(2):171-175.
- Fairbrother G, Siegel MJ, Friedman S, Kory PD, Butts GC. Impact of financial incentives on documented immunization rates in the inner city: results of a randomized controlled trial. *Ambul Pediatr.* 2001;1(4):206-212.
- Giuffrida A, Gosden T, Forland F, et al. Target payments in primary care: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev.* 2000;3:CD000531.

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**41. Uscher-Pines L, Barnett DJ, Sapsin JW, Bishai DM, Balicer RD.**

A systematic analysis of influenza vaccine shortage policies. *Public Health*. 2008;122(2):183-191.

**42. Ransom J, Bashir Z, Phillips C.** Local health department responses during the 2004-2005 influenza vaccine shortage. *J Community Health*. 2007;32(4):283-297.

**43. Mody L, Langa KM, Malani PN.** Impact of the 2004-2005 influenza vaccine shortage on immunization practices in long-term care facilities. *Infect Control Hosp Epidemiol*. 2006;27(4):383-387.

**44. Mossad SB.** Demystifying FluMist, a new intranasal, live influenza vaccine. *Cleve Clin J Med*. 2003;70(9):801-806.

**45. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer**

**PS, Wright PF.** A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis*. 1994;169(1):68-76.

**46. Nichol KL, Mendelman PM, Mallon KP, et al.** Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. *JAMA*. 1999;282(2):137-144.

**47. Treanor JJ, Kotloff K, Betts RF, et al.** Evaluation of trivalent, live, cold-adapted (CAIV-T), and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. *Vaccine*. 1999;18(9-10):899-906. ■