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

Lisa A. Prosser, PhD; Martin I. Meltzer, PhD; Anthony Fiore, MD, MPH; Scott Epperson, MPH; Carolyn B. Bridges, MD; Virginia Hinrichsen, MS, MPH; Tracy A. Lieu, MD, MPH

Objective: To evaluate the effect of adverse events associated with live attenuated influenza vaccine (LAIV) in children younger than 5 years on the cost-effectiveness of influenza vaccination.

Design: A decision analytic model was developed to predict costs and health effects of no vaccination, vaccination with LAIV, and vaccination with inactivated influenza vaccine (IIV). Probabilities, costs, and quality adjustments for uncomplicated influenza, outpatient visits, hospitalizations, deaths, vaccination, and vaccine adverse events were based on primary and published data. The analysis included the possible increased incidence of adverse events following vaccination with LAIV for children younger than 5 years, including fever, wheezing, and hospitalization. A societal perspective was used. Sensitivity analyses, including probabilistic sensitivity analysis, were conducted.

Setting: Vaccination in the physician office setting in the United States.

Participants: Hypothetical cohorts of healthy children aged 6 months to 4 years.

Intervention: Vaccination with LAIV or IIV.

Main Outcome Measure: Incremental cost-effectiveness ratio in dollars per quality-adjusted life-year (QALY).

Results: Cost-effectiveness ratios ranged from $20,000/QALY (age 6-23 months) to $33,000/QALY (age 3-4 years) for LAIV and from $21,000/QALY to $37,000/QALY for IIV for healthy children aged 6 months to 4 years. Inclusion of possible new adverse events for LAIV had varying effects on cost-effectiveness results. Results were not sensitive to the inclusion of wheezing as an adverse event but were sensitive to a possible increase in the probability of hospitalization.

Conclusion: Live attenuated influenza vaccine had comparable cost-effectiveness compared with IIV for children younger than 5 years under a wide range of assumptions about the incidence of adverse events.


Live attenuated influenza vaccine (LAIV) is approved for children 2 years or older without a history of wheezing or asthma. A recent randomized controlled trial among children younger than 5 years of age found that intranasal LAIV was more effective in preventing laboratory-confirmed influenza compared with inactivated influenza vaccine (IIV), yet these data also suggested an increase in adverse events, such as wheezing, in children younger than 5 years of age who receive LAIV compared with IIV. Given that a possible increase in adverse events was of potential concern to providers and parents, we sought to evaluate the effect of these events on cost-effectiveness results. The objective of this study was to evaluate the cost-effectiveness of LAIV using new data on adverse events.

METHODS

We used a previously validated simulation model, built using standard software (TreeAge Pro 2007 Software, release 1.2; TreeAge Software, Williamstown, Massachusetts), to estimate the effect of influenza vaccination on influenza-related health outcomes and costs among children. The decision tree evaluates 3 options: (1) no vaccination; (2) IIV; and (3) LAIV. A simplified schematic of the decision tree is shown in the Figure. Healthy children

Author Affiliations are listed at the end of this article.
were divided into subgroups by age: 6 to 23 months, 2 years (24-35 months), and 3 to 4 years. We used a time frame of 1 year but also included the long-term effects of influenza and influenza vaccines (eg, death, long-term sequelae of influenza-related illness, and vaccine-related adverse effects). All effects lasting more than 1 year were discounted at 3% per year. We used a societal perspective. Event probabilities, by age and risk group, were derived from the published literature and were supplemented by expert opinion where data were limited or unavailable (Table 1 and eTable 1 and eTable 2, http://www.archpediatrics.com). Additional details of the model structure are available in the eAppendix and have been published previously.4 Modifications to the model specific to this analysis are described later.

VACCINATION-RELATED ADVERSE EVENTS

This analysis incorporated medically attended wheezing episodes and hospitalization following wheezing, in addition to 4 adverse events included in previous analyses (eAppendix).3,5,22,23 Trial data1 included a slight increase in all-cause hospitalization for LAIV compared with IIV, although these increases were not statistically significant; therefore, these probabilities were included in the current analysis as a parameter range that included zero.

COSTS

Costs included direct medical and opportunity costs (parent travel, waiting, and visit time)5 (Table 1 and eTable 1) The costing year of the analysis was 2006; all costs were adjusted to 2006 US dollars.25 Costs of influenza-related hospitalizations were updated to reflect new data available for costs of influenza-related hospitalizations in children.25

HEALTH OUTCOMES

The model projected 4 different outcomes that were averted through vaccination: influenza episodes, hospitalizations, deaths, and loss of quality-adjusted life-years (QALYs). A QALY attempts to measure a patient’s physical health and well-being, including the ability to engage in “normal,” everyday activities. The QALYs lost to a disease or condition, therefore, measure the overall reduction in a patient’s well-being, or health-related quality of life, due to an episode of disease and its consequences. We obtained QALY valuations for influenza-related and vaccination-related events from published studies conducted by us and from published data24,27,37,38 (Table 1). A value for the QALYs lost because of an episode of wheezing in a child was not available. We, therefore, used a published estimate of the QALYs lost...
because of wheezing in an adult experiencing an episode of acute asthma.34

ANALYSIS

The primary outcome measure was the incremental cost-effectiveness ratio in dollars per QALY saved for vaccination compared with no vaccination (eAppendix). Secondary measures included costs of vaccination and clinical influenza-related events averted per 1000 vaccinated children, dollars per influenza-related event avoided, dollars per hospitalization avoided, and dollars per death averted. One-way sensitivity analyses were conducted on all variables, in which the impact on the cost-effectiveness ratio was examined by altering each variable within the range of given values (Table 1). We also conducted a sensitivity analysis that examined the effect of increasing all-cause hospitalization following vaccination with LAIV (ie, a possible vaccine-related adverse effect). A probabilistic sensitivity analysis was also conducted (ie, a Monte Carlo analysis was conducted).

RESULTS

HEALTH BENEFITS, RISKS, AND COSTS

For lower-risk children aged 2 to 4 years, LAIV was projected to avert more episodes of influenza, influenza-related hospitalizations, and deaths than IIV per 1000 children vaccinated. However, adverse events were projected to be higher for LAIV than for IIV. All vaccination strategies had a net health benefit compared with no vaccination, as measured by QALYs gained. Costs of vaccination were projected to be higher for LAIV compared with IIV, reflecting both higher costs of the vaccine dose and higher probabilities of adverse events and associated costs for LAIV (Table 2).
Distributions were defined using the most likely, minimum, and maximum values for each parameter and assuming log-normal distributions for costs (see eAppendix [http://www.archpediatrics.com] for defined distributions). In such a Monte Carlo sensitivity analysis, the model is run numerous times, and at the start of each run, the model randomly picks a different value for each variable derived from preset probability distributions. The model was run 10,000 times for each age-risk group and vaccine combination. The output from these probabilistic sensitivity analyses provided CIs (ie, 2.5th and 97.5th percentiles) around the mean values.

Table 1. Modeling Assumptions and Simulation Inputs (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Most Likely Estimate</th>
<th>Range for Sensitivity Analysis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination-related adverse events, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing episode</td>
<td>186</td>
<td>118-220</td>
<td>30,31 and Expert panel</td>
</tr>
<tr>
<td>Quality adjustments (disutility associated with an event)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episode of influenza</td>
<td>0.005</td>
<td>0.002-0.009</td>
<td>32</td>
</tr>
<tr>
<td>Hospitalization, pneumonia</td>
<td>0.076</td>
<td>0.054-0.100</td>
<td>33</td>
</tr>
<tr>
<td>Wheezing episode</td>
<td>0.0018</td>
<td>0.0003-0.005</td>
<td>34</td>
</tr>
<tr>
<td>Hospitalization following vaccination</td>
<td>0.076</td>
<td>0.054-0.100</td>
<td>33</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0.02</td>
<td>0.006-0.041</td>
<td>32</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>0.141</td>
<td>0.092-0.199</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 2. Health Benefits, Risks, and Costs of Influenza Vaccination for Lower-Risk Children Aged 6 Months to 4 Years a,b

<table>
<thead>
<tr>
<th>Per 1000 Children</th>
<th>Mean, $</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Vaccination Program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>105,000</td>
<td>34,000</td>
</tr>
<tr>
<td>IIV</td>
<td>97,000</td>
<td>34,000</td>
</tr>
<tr>
<td>Age 2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>88,000</td>
<td>24,000</td>
</tr>
<tr>
<td>IIV</td>
<td>79,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Age 3-4 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>80,000</td>
<td>13,000</td>
</tr>
<tr>
<td>IIV</td>
<td>73,000</td>
<td>11,000</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; QALY, quality-adjusted life-year.

a Derived from Monte Carlo simulations. In such an analysis, the values of many parameters are altered simultaneously, with the values for each altered parameter derived from preset probability distributions. Input parameters for probabilities, costs, and outcomes were described using probability distributions. Distributions were defined using the most likely, minimum, and maximum values for each parameter and assuming log-normal distributions for costs (see eAppendix [http://www.archpediatrics.com] for defined distributions). In such a Monte Carlo sensitivity analysis, the model is run numerous times, and at the start of each run, the model randomly picks a different value for each variable derived from preset probability distributions. The model was run 10,000 times for each age-risk group and vaccine combination. The output from these probabilistic sensitivity analyses provided CIs (ie, 2.5th and 97.5th percentiles) around the mean values.

b Figures may not sum because of rounding.

c Includes time costs associated with vaccination.

d Includes injection site reactions, systemic reactions, anaphylaxis, and Guillain-Barré syndrome.

e Age groups covered by the licensure currently approved by the US Food and Drug Administration for LAIV are healthy individuals aged 2 to 49 years.
COST-EFFECTIVENESS

For lower-risk children aged 2 and 3 to 4 years, vaccination with either IIV or LAIV resulted in a net cost both in terms of cost per influenza episode averted and cost per QALY saved (Table 2 and Table 3). In 1-way sensitivity analyses, results were not sensitive to variables representing incidence, cost, or quality adjustment for wheezing following vaccination with LAIV (eFigure 1). Cost-effectiveness ratios were most sensitive to changes in the probability of influenza illness, probability of influenza-related hospitalizations, and total vaccination costs (eFigure 1). For a possible increase in the probability of all-cause hospitalization following vaccination with LAIV greater than 0.006, IIV would become the preferred strategy because LAIV would become more costly and save fewer QALYs (ie, LAIV is dominated by IIV) as this probability increased (eFigure 2 and eTable 4).

MAJOR FINDINGS

Vaccinating lower-risk children using either LAIV or IIV did not generate cost savings but yielded cost-effectiveness ratios less than $40,000 per QALY gained for children aged 6 months to 4 years. For children in this age group, vaccination with LAIV yielded slightly more favorable mean cost-effectiveness ratios than IIV under a wide range of assumptions about the incidence of adverse events but confidence intervals for cost-effectiveness ratios were overlapping for the 2 vaccination strategies. We found the addition of wheezing-related adverse events had little impact on the cost-effectiveness of vaccination with LAIV (Table 3). Even after the inclusion of wheezing-related adverse events, vaccination with LAIV resulted in health benefits that outweighed vaccine adverse events as measured by QALYs.

COMMENTS

These findings are similar to results from a previous analysis using an earlier version of this simulation model. The current analysis revised the previous model to incorporate newly identified potential adverse events for LAIV, revised assumptions regarding the relative incidence of previously identified adverse events for LAIV and IIV, and new data on the costs of influenza-related hospitalizations for children. The key findings remain robust to the inclusion of new data on adverse events and hospitalization costs: cost-effectiveness ratios for vaccination of healthy children younger than 5 years are favorable compared with other well-accepted pediatric interventions. These results are also consistent with other published analyses of influenza vaccination in children that also demonstrated cost savings or cost-effective results for vaccination in similar age groups but that did not consider new adverse events.

One potential limitation of this analysis is the exclusion of herd immunity effects. If these effects were considered, they would likely result in more favorable cost-effectiveness ratios for vaccination options. In addition, published data were not available for some key variables, such as quality adjustments for a wheezing episode and hospitalizations following vaccination, and our analysis used values from similar health states not associated with vaccination. The current analysis assumes that hospitalizations following vaccination have the same loss in quality of life associated with an influenza-related hospitalization. However, parents may place a greater value for the loss in quality of life due to a vaccination-related adverse event and that loss would not be fully captured herein.

We used data on the loss in QALYs associated with wheezing events in adults because values for children were not available. This approach may underestimate the loss in quality of life associated with wheezing in children, because we have shown that respondents valued influenza health states in children as associated with a greater loss in quality of life (L.A.P., K. Payne, PhD, D. Rusnak, BA, P. Shi, MA, T. Uyeki, MD, MPH, M. Messonnier, PhD, “Value in Health,” unpublished data, December 2007); however, sensitivity analysis for this parameter did not demonstrate a substantial effect on results.

This analysis assumes that vaccine effectiveness does not vary by age whereas recent data have suggested that the relative effectiveness of LAIV compared with IIV may be greater in very young children. This would have some effect on cost-effectiveness ratios as demonstrated by 1-way sensitivity analyses that indicate that cost-effectiveness ratios could vary as much as 25% to 50% when using the upper and lower bounds of plausible ranges for vaccine effectiveness. However, given the substantial uncertainty associated with the base case estimates (Table 2 and Table 3), the main conclusion that the cost-effectiveness ratios for LAIV and IIV are not significantly different would likely hold even for the younger
The cost-effectiveness of influenza vaccination for children remains favorable when considering new data for vaccine adverse effects. Cost-effectiveness ratios were comparable for LAIV and IIV for low-risk children aged 6 months to 4 years. Postlicensing safety studies of both LAIV and IIV in children should continue to monitor wheezing-related adverse events, including all-cause hospitalization.

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Author Affiliations: Child Health Evaluation and Research Unit, Division of Pediatrics, University of Michigan Health System, Ann Arbor (Dr Prosser); Center for Child Health Care Studies, Department of Population Medicine (Drs Prosser and Lieu and Ms Hinrichsen), Harvard Medical School and Harvard Pilgrim Health Care, Boston, Massachusetts; and Division of Emerging Infections and Surveillance Services, National Center for Preparedness Detection and Control of Infectious Diseases, and Coordinating Center for Infectious Diseases (Dr Meltzer), and Influenza Division (Drs Fiore and Bridges and Mr Epperson), Centers for Disease Control and Prevention, Atlanta, Georgia.

Correspondence: Lisa A. Prosser, PhD, Division of General Pediatrics, University of Michigan Health System, 300 N Ingalls St, Room 6E14, SPC 5456, Ann Arbor, MI 48109 (lisapros@med.umich.edu).

Author Contributions: Study concept and design: Prosser, Meltzer, Fiore, Bridges, and Lieu. Acquisition of data: Prosser, Meltzer, Epperson, Bridges, and Hinrichsen. Analysis and interpretation of data: Prosser, Meltzer, Fiore and Bridges. Drafting of the manuscript: Prosser, Meltzer, and Fiore. Critical revision of the manuscript for important intellectual content: Prosser, Meltzer, Fiore, Epperson, Bridges, Hinrichsen, and Lieu. Statistical analysis: Prosser and Meltzer. Obtained funding: Prosser, Fiore, Bridges, and Lieu. Administrative, technical, and material support: Epperson, Bridges, Hinrichsen, and Lieu. Study supervision: Prosser and Fiore.

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**REFERENCES**


Correction

Error in Text. In the Article titled “Hour-Specific Bilirubin Nomogram in Infants With ABO Incompatibility and Direct Coombs-Positive Results” by Schutzman et al, published in the December 2010 issue of the Archives (2010;164[12]:1138-1164), an error occurred in the text on page 1162. The third and fourth sentences of the second paragraph in the right-hand column should have read, “They determined that, at the postnatal age of 6 hours, a serum bilirubin level greater than 4 mg/dL (to convert to micromoles per liter, multiply by 17.104) was a strong predictor of significant hyperbilirubinemia, ie, that the infant would require phototherapy. They found that a serum bilirubin level greater than 6 mg/dL at the postnatal age of 6 hours was a good predictor of severe hemolytic disease, ie, that the infant would require additional modalities such as intensive phototherapy, intravenous immunoglobulin, or exchange transfusion.” This article was corrected online.