Estimating Efficacy of Trivalent, Cold-adapted, Influenza Virus Vaccine (CAIV-T) against Influenza A (H1N1) and B Using Surveillance Cultures

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The authors report on a community-based, nonrandomized, open-label study, conducted during the 2000–2001 influenza season in Temple-Belton, Texas, of the protective effectiveness of trivalent, cold-adapted, influenza virus vaccine (CAIV-T) in children aged 18 months–18 years. The dominant circulating strains in 2000–2001 were influenza A/New Caledonia/20/99 (H1N1) and influenza B/Sichuan/379/99. Children had access to CAIV-T during the 1998–1999, 1999–2000, and 2000–2001 influenza seasons. The vaccine included influenza A/Sydney/5/97 (H3N2) and B/Beijing/184/93-like (B/Ann Arbor/1/94) strains in all three seasons. The vaccine included A/Beijing/262/95 (H1N1) in 1998–1999 and 1999–2000, which was replaced by A/New Caledonia/20/99 (H1N1) in 2000–2001. When medically attended acute respiratory illness (MAARI) was used as the outcome, the protective effectiveness for children vaccinated in 2000 was 18% (95% confidence interval (CI): 11, 25). Based on a combination of a validation sample of surveillance cultures and the MAARI outcome, protective efficacy against combined influenza A (H1N1) and B was 79% (95% CI: 51, 91). The efficacy estimate, after accounting for missing influenza culture status, against influenza A (H1N1) alone was 92% (95% CI: 42, 99) and against a new variant of influenza B alone was 66% (95% CI: 9, 87). CAIV-T provides substantial protection against a mixture of influenza A (H1N1) and B. Results demonstrate the powerful potential of using validation sets for outcomes in vaccine field studies.

culture; data collection; data interpretation, statistical; influenza A virus; influenza B virus; influenza vaccine; vaccines; vaccines, attenuated

Abbreviations: CAIV-T, trivalent, cold-adapted, influenza virus vaccine; CI, confidence interval; MAARI: medically attended acute respiratory illness; VESₚ, protective vaccine efficacy; VESᵥ, vaccine effectiveness estimated by using MAARI as the outcome; VESₛᵥ, vaccine efficacy estimated by using surveillance cultures with the mean score method.

Editor’s note: An invited commentary on this article is published on page 312.

The live-attenuated, trivalent, cold-adapted, influenza virus vaccine (CAIV-T) was recently licensed for persons aged 5–49 years in the United States. CAIV-T is administered as a nasal spray. In a randomized, placebo-controlled trial in children aged 15–71 months, overall efficacy was 92 percent (95 percent confidence interval (CI): 89, 94) in preventing culture-confirmed influenza A (H3N2) and B infections (1–3). Since influenza A (H1N1) did not circulate between the 1995–1996 and 2000–2001 influenza seasons, the efficacy of CAIV-T in preventing recent strains of influenza A (H1N1) in healthy children could not be assessed directly.

A field study of CAIV-T was being conducted during the 2000–2001 influenza season, with the dominant circulating
strains being influenza A/New Caledonia (H1N1) and influenza B/Sichuan. In vaccine field studies, often a nonspecific case definition rather than a more specific confirmatory diagnosis is used as the outcome. However, this method leads to severely attenuated estimates of protection. Halloran and Longini (4) suggested using small samples of confirmed cases to correct the bias in the vaccine estimates based on the nonspecific case definition alone. These methods are used for outcomes in many other types of health studies (5–7).

In this paper, we evaluate the efficacy of CAIV-T against influenza during the influenza season of 2000–2001. For this study, we used surveillance cultures taken from a sample of the participants to obtain more accurate estimates of protective efficacy against influenza than those obtained by using the nonspecific, clinical case definition.

MATERIALS AND METHODS

Field study

A field study was conducted to evaluate the protective efficacy, VE5, of CAIV-T vaccination in healthy children during the 2000–2001 influenza season in Temple-Belton, Texas, and surrounding areas. This study was part of a larger community-based, nonrandomized, open-label field study. The larger field study of CAIV-T was conducted from August 1998 through June 2001 in Temple-Belton as well as two other communities to evaluate the indirect effectiveness of vaccination of healthy children (8, 9).

The Temple-Belton area includes approximately 19,700 children aged 18 months–18 years. Healthy children of this age were offered CAIV-T vaccination at Scott & White clinics from 1998 to 2001. Scott & White is the major health care provider, covering about 80 percent of the population. Advertisement was communitywide, and children did not need to be members of Scott & White to receive CAIV-T. The analysis in this paper includes children who were Scott & White Health Plan members. Healthy children and adolescents aged 18 months–18 years who were not pregnant and were not planning a pregnancy within 6 weeks were eligible to enroll. Other exclusionary criteria have been detailed by Piedra et al. (8). Signed, informed consent was obtained from a parent or legal guardian, and an assent was obtained from children aged 7 years or older who were capable of providing one. The protocol was approved each year by the institutional review boards of Scott & White Clinic, Baylor College of Medicine, and the Texas Department of Health.

Children received a single dose of CAIV-T each year that they were enrolled. The CAIV-T vaccinations of interest in the present analysis were administered in the two influenza seasons 1999–2000 and 2000–2001. The illness data used in our analysis are from influenza season 2000–2001 only. Age-eligible members of the Scott & White Health Plan on January 7, 2001, were considered for inclusion in the analysis. Separate analyses were conducted of data on children who received CAIV-T in the 1999–2000 but not the 2000–2001 season and on children who received CAIV-T in the 2000–2001 season. The two groups included some children who had received additional doses of CAIV-T in previous years as well. Age at time of vaccination was used for those who received CAIV-T during the 2000–2001 season. For those who received CAIV-T in 1999–2000 or never received CAIV-T, the first day of enrollment for the 2000–2001 season, November 6, 2001, was used to compute age. The youngest children vaccinated in the 1999–2000 season were aged 2.5 years by November 6, 2000. Hence, the comparison groups were adjusted to include a similar age group distribution for children less than 5 years of age.

Vaccine

CAIV-T was supplied by Aviron (Mountain View, California), now MedImmune Vaccines Inc., frozen in single-dose nasal spray applicators. The vaccine contained a 10^7 median tissue culture infective dose (TCID50) of each of the three attenuated strains that matched the antigens recommended for trivalent influenza vaccine by the US Food and Drug Administration for the three influenza seasons 1998–1999, 1999–2000, and 2000–2001. The vaccine included influenza A/Sydney/5/97 (H3N2) and B/Beijing/184/93-like (B/Ann Arbor/9/94) strains in all three seasons.

A/Beijing/262/95 (H1N1) was included in the vaccine in 1998–1999 and 1999–2000. In 2000–2001, A/New Caledonia/20/99 (H1N1) replaced A/Beijing/262/95 (H1N1) in the vaccine. The vaccine was stored frozen at −20°C and was thawed to room temperature by holding the applicator in the palm for less than 5 minutes prior to use.

Case definitions

The clinical outcome medically attended acute respiratory illness (MAARI) included all International Classification of Diseases, Ninth Revision, Clinical Modification diagnoses (codes 381–383, 460–487) for upper and lower respiratory tract infections, otitis media, and sinusitis. MAARI outcomes and demographic data were extracted from the Scott & White Health Plan administrative database. For each visit, one or two International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes were listed. Visits for which asthma diagnosis codes alone were noted, without another MAARI code, were excluded. Any child presenting with history of fever and any respiratory illness at the Scott & White clinics was eligible to have a throat swab (or nasal wash in young infants) for influenza virus culture obtained after informed verbal consent as a standard of care. The health care providers obtained the specimens and received the results on their patients. The decision to obtain specimens was made irrespective of whether a patient had received CAIV-T. The influenza A and B viruses were characterized by the National Centers for Disease Control and Prevention (Atlanta, Georgia). This characterization was performed by using the box titration by hemagglutinin inhibition with specific polyclonal antisera raised in ferrets to all of the related variants. The health care providers supplemented this procedure with polymerase chain reaction when necessary and characterized the hemagglutinin gene if necessary.
Statistical data analysis

The risk of developing MAARI was compared among the children receiving CAIV-T and those who had never received CAIV-T. The protective effectiveness of CAIV-T against MAARI was estimated as \( \text{VE}_{S,v} = 1 - \text{RR} \), where RR is the relative risk of MAARI in vaccinated children compared with unvaccinated children (10) and \( \alpha \) is for auxiliary outcome. Age-adjusted estimates were obtained by using sample-size-weighted averages. Confidence intervals were based on the assumption of a normal approximation of the logarithm of the ratio of two independent binomial random variables (11).

Estimates of the protective efficacy of CAIV-T against influenza using the surveillance samples, \( \text{VE}_{S,v} \), were obtained by using the mean score method for auxiliary outcomes (12), an estimating equations approach for handling missing data; \( v \) is for validation sample. The method estimates the score contribution for main study members with only auxiliary outcome data from the mean of the score contributions of a sample of study subjects with the same observed covariate and auxiliary outcome values on whom the specific outcome has been measured. In this analysis, the clinical outcome MAARI was the nonspecific, auxiliary outcome, whereas actual influenza status was the specific outcome of interest. The confidence intervals take into account the uncertainty due to culturing only a sample of the MAARI cases.

The variable \( Y = \text{outcome of interest (influenza status)} \), \( A = \text{auxiliary outcome (MAARI, yes or no)} \), \( X = \text{set of covariates (vaccination, age group)} \), \( P(y | x) = \text{binomial probability model} \), \( \beta = \text{parameters to estimate in the probability model} \), \( S_\beta = \text{score function} \), and \( V, V' = \text{in the validation set or not} \). The estimating equation is

\[
\sum_{i \in V} S_\beta(Y_i | X_i) + \sum_{j \in V'} \hat{E}(S_\beta(Y_j | A_j, X_j)) = 0.
\]

An unbiased estimator for a child who had no culture performed is

\[
\hat{E}(S_\beta(Y_j | A_j, X_j)) = \sum_{i \in V(A_j, X_j)} S_\beta(Y_i | X_i) / n(V(A_j, X_j)).
\]

The variance was estimated on the adjusted log relative risk by using the mean score and multivariate delta methods (12–14). With just one covariate, as in this situation, the model is saturated. Thus, in this instance, the mean score method is equivalent to the semiparametric efficient method (7).

Let \( \Delta = 0,1 \) denote whether influenza status is missing or known. For children positive for MAARI who were sampled for influenza culture, \( \Delta = 1 \). For those positive for MAARI who were not sampled for influenza culture, \( \Delta = 0 \) and influenza status is missing. We assumed that all children negative for MAARI were also negative for influenza disease; thus, \( \Delta = 1 \). The mean score method produces valid estimates if the data are missing at random (12); refer to Little and Rubin (15). In our example, missing at random means that \( Y \) and \( \Delta \) are conditionally independent given \( A \) and \( X \), denoted \( Y \perp \Delta | A, X \). If \( Y \) and \( \Delta \) are conditionally independent given \( (A, X) \), then \( [Y | X, A, \Delta = 1] = [Y | X, A] \), where the brackets denote a probability density distribution (16).

The mean score method can be intuitively understood as producing \( \text{VE}_{S,v} \), point estimates equal to those obtained if the proportion of positive cultures in each group of the surveillance cultures was multiplied by the number of MAARI cases to obtain the expected number of positive influenza cases in each group. The relative risk based on the expected number of influenza cases in the vaccinated and unvaccinated groups would then be used to compute \( \text{VE}_{S,v} \) (4).

A continuity correction of 0.5 was added to the number of cultured samples and the number positive in the age group 1.5–4 years in the analysis of vaccination in both years because no positive cultures were found in the vaccinated group. In this paper, overall \( \text{VE}_{S,v} \) is reported in two ways. The overall estimate is obtained by pooling the data, thus avoiding the continuity correction. The age-adjusted \( \text{VE}_{S,v} \) obtained by using sample-size-weighted averages, the continuity correction in the youngest age group, and the delta method for the variance estimate, is reported in the text. Pearson’s chi-square test was conducted by using version 6 of S-PLUS software (17).

Sensitivity analysis

In this study, sampling of MAARI cases for influenza culture was conducted primarily as surveillance for influenza rather than to confirm individual cases. Since the children selected for cultures did not constitute a random sample, the \( \text{VE}_{S,v} \) estimates based on the mean score method could be biased. A potential source of selection bias was that physicians tend to culture people thought to have the disease of interest, in this instance, influenza. In this case, \( \Delta \) would not be conditionally independent of \( Y \) given \( A, X \), or the data would be nonignorably missing; refer to Little and Rubin (15).

For example, if influenza disease were more severe in unvaccinated than in vaccinated children, then physicians would oversample unvaccinated cases if they sampled more severe cases in the belief that these children had influenza. A sensitivity analysis enables examination of the magnitude of the potential bias. Let \( p_1 \) and \( p_0 \) be the probability of influenza illness in the vaccinated and unvaccinated groups. Let \( q_1 \) and \( q_0 \) be the probability of noninfluenza disease in the vaccinated and unvaccinated groups. Let \( c_1 \) and \( c_0 \) be the fraction of true influenza cases that are severe in the vaccinated and unvaccinated groups. For simplicity, assume that all noninfluenza respiratory disease is not severe. Let \( f = \text{Pr}(\Delta = 1) \) for less severe cases of true influenza and for noninfluenza respiratory disease. Let \( k_f = \text{Pr}(\Delta = 1) \) for severe cases of true influenza. Thus, the possibly biased estimate of \( \text{VE}_{S,v} \), using the surveillance cultures and the MAARI outcomes, will be

\[
\text{VE}_{S,v} = 1 - \frac{(1 - c_1)p_1 + kc_1p_1}{q_1 + (1 - c_1)p_1 + kc_1p_1} \frac{[q_1 + p_1]}{q_0 + (1 - c_0)p_0 + kc_0p_0} \frac{[q_0 + p_0]}{(1 - c_0)p_0 + kc_0p_0}. \tag{1}
\]

Equation 1 reduces to \( \text{VE}_f = 1 - p_1 / p_0 \), the true efficacy, if \( k = 1 \), that is, there is no oversampling of severe cases.
Whether the estimate $VE_{S,v}$, taking missing influenza status into account, is biased upward or downward relative to the true efficacy $VE_S$ depends on the relation of the values $p_1$, $p_0$, $q_1$, $q_0$, $c_0$, $c_1$, and $k$. We make the following assumptions: $p_1 < p_0$, $c_1 < c_0$, $k > 1$. To look at the potential bounds of the bias, we present the worst-case situation in which no vaccinated influenza cases are severe ($c_1 = 0$) and all unvaccinated influenza cases are severe ($c_0 = 1$) with differential sampling.

Under randomization, equal exposure would be expected in the vaccinated and unvaccinated groups to both influenza and noninfluenza disease. In this instance, $q_1 = q_0 = q$. In observational vaccine field studies, the potential unmeasured confounders of particular interest are whether the vaccinated and unvaccinated groups are different with respect to exposure to infection or underlying susceptibility. Unmeasured confounders could bias the efficacy estimate even if every suspected case were cultured. Since our study was observational, there may have been a difference in the two groups between exposure or susceptibility to either influenza disease or noninfluenza disease, so possibly $q_1 \neq q_0$.

RESULTS

Table 1 shows the distribution of age, gender, and prior asthma disease for each group of children. Table 2 contains information on the number of children, the number of MAARI, the number of cultures performed, and the number of cultures positive for each group. The overall fraction of MAARI cases sampled was somewhat higher in the unvaccinated than in the vaccinated groups for those vaccinated in 2000 ($p = 0.03$) but not significantly for those vaccinated in 1999 ($p = 0.47$). As expected, the proportion of cultures that were positive was consistently higher in the unvaccinated than in the vaccinated groups.

The protective efficacy estimates against influenza, taking missing influenza status into account, were much higher than the estimates of the protective effects of CAIV-T against MAARI (table 3). Although the point estimates were higher, the confidence intervals were wider because of the uncertainty resulting from not culturing all MAARI cases. For children vaccinated in 2000, sample-size-weighted $VE_{S,v} = 0.77$ (95 percent CI: 0.48, 0.90). For children vaccinated in 1999, $VE_{S,v} = 0.62$ (95 percent CI: 0.09, 0.85). Both were slightly lower than the unadjusted values reported in table 3.

Influenza A (H1N1) and B circulated in the study community, as seen nationwide in the United States in 2000–2001. All influenza A variants were subtyped H1N1. All viruses in CAIV-T recipients were characterized by the Centers for Disease Control and Prevention as New Caledonia (H1N1) and B/Sichuan. Of the five positive cultures from cases vaccinated in 2000, four were influenza B and one was influenza A (H1N1). Of the four positive cultures from cases vaccinated in 1999, three were influenza B and one was influenza A (H1N1).

Of the 133 positive cultures from the never-vaccinated cases, 65 were influenza B and 68 were influenza A (H1N1). Although the number of positive cultures from the vaccinated cases was small, the efficacy estimates, accounting for missing influenza status, for influenza A (H1N1) were 0.92 (95 percent CI: 0.42, 0.99) for those vaccinated in 2000 and 0.84 (95 percent CI: –0.11, 0.98) for those vaccinated in 1999. For influenza B, the corresponding estimates were 0.66 (95 percent CI: 0.09, 0.87) and 0.50 (95 percent CI: –0.49, 0.83).

In the sensitivity analysis, we initially assumed the worst-case situation in which no influenza in vaccinated cases was severe and all influenza in unvaccinated cases was severe, and that severe cases were oversampled. In the first instance, we assumed that the probability of noninfluenza disease was equal in the vaccinated and unvaccinated groups ($q_1 = q_0 = q$). Then, our estimated $VE_{S,v} = 0.79$ for children vaccinated in 2000, taking missing influenza status into account, could correspond to a true efficacy of $VE_S = 0.71$ if severe cases were $k = 1.5$ times oversampled and to a true efficacy of $VE_S = 0.64$ if $k = 2$. If just half and 1/16 of the influenza in unvaccinated and vaccinated cases was severe, then true efficacy was $VE_S = 0.75$ if $k = 1.5$ and $VE_S = 0.72$ if $k = 2$. Under the assumption that $q_0 \neq q_1$, the results were quite similar. For example, if no influenza in vaccinated cases was severe and all influenza in unvaccinated cases was severe, then the true

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccinated in 2000 (n = 2,281)</th>
<th>Vaccinated in 1999 (n = 531)</th>
<th>Not vaccinated (n = 9,325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5–4</td>
<td>24</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>5–9</td>
<td>35</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>10–18</td>
<td>41</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>Male gender</td>
<td>51</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Prior asthma disease</td>
<td>1.3</td>
<td>0.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* All values are expressed as percentages.
† Some children had received trivalent, cold-adapted, influenza virus vaccine in previous years as well.
‡ Number of children in each group by vaccine status.
Influenza Vaccine Efficacy Using Virus Cultures

VE = 0.73 if \( k = 1.5 \) and VE = 0.66 if \( k = 2 \). If just half and 1/16 of the influenza in unvaccinated and vaccinated cases was severe, VE = 0.76 if \( k = 1.5 \) and VE = 0.74 if \( k = 2 \). In other words, in most plausible scenarios consistent with the data in this study, the upward bias due to physicians over-sampling true influenza cases of the estimated VE, taking missing influenza status into account, compared with the true efficacy is not more than 10 percent. Even if the data on influenza status are not missing at random, true efficacy for those vaccinated in 2000 was likely much higher than the estimated effectiveness of VE = 0.18 based on the nonspecific MAARI outcome alone.

### TABLE 2. Study data for influenza epidemic season 2000–2001, by age and vaccine group, Temple-Belton, Texas

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Vaccine</th>
<th>No. of children</th>
<th>No. of MAARI† cases</th>
<th>MAARI attack rate</th>
<th>No. of MAARI cases cultured</th>
<th>No. of positive cultures</th>
<th>Fraction of cultures positive</th>
<th>Fraction cultured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Vaccinated in 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5–4</td>
<td>CAIV-T†</td>
<td>537</td>
<td>389</td>
<td>0.72</td>
<td>16</td>
<td>0</td>
<td>0.041</td>
<td>0.041</td>
</tr>
<tr>
<td>5–9</td>
<td>CAIV-T</td>
<td>807</td>
<td>316</td>
<td>0.39</td>
<td>17</td>
<td>2</td>
<td>0.12</td>
<td>0.054</td>
</tr>
<tr>
<td>10–18</td>
<td>CAIV-T</td>
<td>937</td>
<td>219</td>
<td>0.23</td>
<td>19</td>
<td>3</td>
<td>0.16</td>
<td>0.087</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2,281†</td>
<td>924</td>
<td>0.41</td>
<td>52</td>
<td>5</td>
<td>0.10</td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>8,662</td>
<td>3,549</td>
<td>0.41</td>
<td>327</td>
<td>133</td>
<td>0.41</td>
<td>0.077</td>
</tr>
<tr>
<td><strong>Vaccinated in 1999 but not in 2000</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5–4</td>
<td>CAIV-T</td>
<td>148</td>
<td>87</td>
<td>0.59</td>
<td>2</td>
<td>0</td>
<td>0.023</td>
<td>0.023</td>
</tr>
<tr>
<td>5–9</td>
<td>CAIV-T</td>
<td>285</td>
<td>113</td>
<td>0.40</td>
<td>9</td>
<td>1</td>
<td>0.11</td>
<td>0.080</td>
</tr>
<tr>
<td>10–18</td>
<td>CAIV-T</td>
<td>498</td>
<td>131</td>
<td>0.26</td>
<td>15</td>
<td>3</td>
<td>0.20</td>
<td>0.115</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>931§</td>
<td>331</td>
<td>0.36</td>
<td>26</td>
<td>4</td>
<td>0.15</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>8,662</td>
<td>3,549</td>
<td>0.41</td>
<td>327</td>
<td>133</td>
<td>0.41</td>
<td>0.092</td>
</tr>
</tbody>
</table>

* Number in each group by vaccine status.
† MAARI, medically attended acute respiratory illness; CAIV-T, trivalent, cold-adapted, influenza virus vaccine.
‡ 848 children received CAIV-T in 2000 only.
§ 616 children received CAIV-T in 1999 only.

### TABLE 3. Vaccine effectiveness (VE\(_{a,a}^*)\) against MAARI and vaccine efficacy (VE\(_{a,v}^*)\) against combined influenza A (H1N1) and B after considering missing influenza status, influenza epidemic season 2000–2001, Temple-Belton, Texas

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>VE(_{a,a}^*) MAARI</th>
<th>95% CI(^*)</th>
<th>VE(_{a,v}^*) influenza</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccinated in 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5–4</td>
<td>0.20</td>
<td>0.14, 0.25</td>
<td>0.91</td>
<td>–0.34, 0.99</td>
</tr>
<tr>
<td>5–9</td>
<td>0.25</td>
<td>0.15, 0.34</td>
<td>0.80</td>
<td>0.26, 0.95</td>
</tr>
<tr>
<td>10–18</td>
<td>0.14</td>
<td>0.01, 0.26</td>
<td>0.70</td>
<td>0.13, 0.90</td>
</tr>
<tr>
<td>Total</td>
<td>0.18</td>
<td>0.11, 0.24</td>
<td>0.79</td>
<td>0.51, 0.91</td>
</tr>
<tr>
<td><strong>Vaccinated in 1999 but not in 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5–4</td>
<td>0.29</td>
<td>0.15, 0.42</td>
<td>0.50</td>
<td>–0.19, 0.96</td>
</tr>
<tr>
<td>5–9</td>
<td>0.23</td>
<td>0.09, 0.38</td>
<td>0.81</td>
<td>–0.22, 0.97</td>
</tr>
<tr>
<td>10–18</td>
<td>0.03</td>
<td>–0.13, 0.18</td>
<td>0.57</td>
<td>–0.21, 0.85</td>
</tr>
<tr>
<td>Total</td>
<td>0.12</td>
<td>0.03, 0.22</td>
<td>0.67</td>
<td>0.18, 0.87</td>
</tr>
</tbody>
</table>

* VE\(_{a,v}^*\), vaccine effectiveness estimated by using medically attended acute respiratory illness (MAARI) as the outcome; VE\(_{a,a}^*\), vaccine efficacy estimated by using surveillance cultures with the mean score method; CI, confidence interval.
We demonstrated substantial efficacy of CAIV-T against influenza during an epidemic of influenza A (H1N1) and B. Although the numbers were small, the efficacy of CAIV-T was likely as high against influenza A (H1N1) as it was against influenza B. Furthermore, protection was effective against influenza A (H1N1) and B more than a year after vaccination since children who were last vaccinated in 1999 were substantially protected during the 2000–2001 influenza season. Our efficacy estimate for influenza A (H1N1), accounting for missing influenza status, for those vaccinated in 2000 compares favorably with a previous estimate of 0.76 (95 percent CI: 0.58, 0.87) for culture-confirmed influenza A (H1N1) illness from a randomized trial of cold-adapted and inactivated influenza A vaccine (18). Our efficacy estimate, accounting for missing influenza status for influenza B, for those vaccinated in 2000 was lower than the previous estimate of 0.92 (95 percent CI: 0.82, 0.96) for culture-confirmed influenza B in a randomized trial of CAIV-T (3), but our confidence interval was wide.

Our results provide evidence for broad immunity of CAIV-T across the new influenza variants A/New Caledonia (H1N1) and B/Sichuan that circulated during the 2000–2001 influenza season. CAIV-T containing A/Beijing (H1N1) virus, administered to children in 1999, gave good cross-protection against A/New-Caledonia (H1N1) virus during the 2000–2001 season (VE\textsubscript{S,v} = 0.84). In addition, CAIV-T containing B/Beijing, given to children in 2000, appears to have provided good protection against B/Sichuan virus during the 2000–2001 influenza season (VE\textsubscript{S,v} = 0.66).

Statistical methods that use specific measures in small samples of the study subjects to correct bias when nonspecific measures are used in the main study are used in other epidemiologic fields. This is the first known study to demonstrate the powerful potential of these methods in vaccine field studies (4). As shown here, use of information from the surveillance cultures produces estimates of protective efficacy against influenza illness more in agreement with results from randomized, placebo-controlled trials than did use of the nonspecific case definition alone. The added uncertainty from not culturing all of the MAARI cases is taken into account with the statistical method (12).

In this study, selection of children with MAARI for influenza culture was not random. Surveillance cultures were performed at the discretion of the health care provider. Influenza status and probability of being sampled might not have been conditionally independent of MAARI status and the covariates, which would have violated the conditions for the mean score method to provide valid estimates of protective efficacy. Physicians might have tended to choose for culturing those MAARI cases that they believed had influenza. If influenza disease was more moderate in the vaccinated group, then oversampling in the unvaccinated group might have occurred based on influenza status, which was not measured for everybody. If so, the missing at random assumption was violated. Our sensitivity analysis demonstrated that, under most plausible scenarios, the probable upward bias of the VE\textsubscript{S,v} estimate compared with the true VE\textsubscript{S} due to physicians oversampling severe cases was not very large compared with if all suspected cases had been cultured. The true efficacy would still be much higher than the estimate based on the nonspecific outcome alone.

If physicians know vaccination status, they might oversample either the unvaccinated or the vaccinated children. They might tend to think that vaccinated children would not have influenza and therefore oversample the unvaccinated children. However, oversampling due to knowledge of vaccination status alone would not bias the estimate since the estimation procedure stratifies on the vaccination status of the child. Therefore, in this instance, the data would be missing at random (19). In fact, in future studies, it would be desirable to oversample the vaccinated, nonspecific cases for culturing. Oversampling in the vaccinated group would help avoid having zero positive cultures in the vaccinated groups (14).

The consistently higher proportion of positive cultures in the unvaccinated groups could have been partly due to vaccinated cases with influenza being less likely than unvaccinated cases to be culture positive. However, this scenario would produce exactly the same bias that would be obtained if all of the MAARI cases had been cultured, as in many randomized, double-blinded vaccine trials (1–3, 18).

Future vaccine field studies that use validation samples could be intentionally designed so that the specific outcome would be missing at random within any given observed stratum of the study subjects. The sample size needed in the validation sample to correct the bias from using the nonspecific outcome is not necessarily large. In this case, the overall sampling fraction was well below 10 percent. However, with a highly efficacious vaccine, oversampling in the vaccinated groups might be needed. Other nonspecific outcomes, such as otitis media, could also be used. Further challenges concerning influenza and other infectious diseases will include more temporal detail and use time-to-event data in the analysis. Since the study takes place during an epidemic, the probability that a MAARI case will be a true influenza case changes rapidly from week to week. This issue requires further research.

In conclusion, when the vaccine strains antigenically match the circulating strains, CAIV-T can provide strong protection (VE\textsubscript{S} > 90 percent), as shown in this study and another study in children (1–3). In addition, CAIV-T could still provide substantial protection (50 percent < VE\textsubscript{S} < 90 percent) even though the vaccine strains did not antigenically match the circulating strains, as shown in this study and another study in children (2, 3).

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