Background: Influenza B viruses from 2 lineages cocirculate annually. Because the single B strain contained in trivalent vaccines may not match the major circulating strain, adding a second B virus could enhance protection. This study compared the safety and immunogenicity of an investigational quadrivalent Ann Arbor strain live attenuated influenza vaccine (Q/LAIV) with that of 2 trivalent vaccines (T/LAIV), each containing a B strain from a different lineage.

Methods: This randomized, double-blind study was designed to demonstrate the immunologic noninferiority of Q/LAIV compared with T/LAIV in children 2–17 years of age by comparing postdose geometric mean titers of hemagglutination inhibition antibodies. Children were randomized 3:1:1 to receive Q/LAIV or 1 of 2 T/LAIV vaccines. Those subjects who were 9–17 years of age received 1 dose, and those 2–8 years of age received 2 doses 1 month apart. Serum immune responses were evaluated 1 month after dose 1 (dose 2 for influenza vaccine–naïve subjects aged 2–8 years).

Results: Q/LAIV was noninferior to T/LAIV: upper bounds for all four 95% confidence intervals for the postdose geometric mean titer ratios (T/LAIV divided by Q/LAIV) were ≤1.5, the predefined noninferiority margin. The overall seroresponse rates (4-fold rise) were comparable between treatment groups. Safety events were comparable, except that fever was more common after dose 1 in Q/LAIV subjects (5.1%) than in T/LAIV subjects (3.1%) 2–8 years of age.

Conclusions: The immunogenicity of Q/LAIV was noninferior to that of T/LAIV in children aged 2–17 years; safety was also comparable. Q/LAIV may broaden the protection against influenza B strains provided by current trivalent influenza vaccines.

Key Words: quadrivalent, influenza vaccine, immunogenicity, clinical trial, children, intranasal

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Immunogenicity and Safety of a Quadrivalent Live Attenuated Influenza Vaccine in Children

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The primary objective of this randomized, controlled, double-blind, multicenter study was to assess the noninferiority of the immune response after Q/LAIV dosing to that after dosing with matching T/LAIV vaccines by comparing postdose geometric mean titers (GMTs) of serum hemagglutination inhibition (HAI) antibodies for the 4 vaccine strains. Secondary objectives included between-group comparisons of HAI antibody seroresponse, achievement of HAI antibody titer ≥2, and safety and tolerability. The study protocol and informed consent documents were approved by the institutional review board for each site, and written informed consent was provided by each subject’s parent or legal guardian (with age-appropriate assent from the child) after the nature and possible consequences of the study were explained. This study was conducted in accordance with the Declaration of Helsinki and was registered on ClinicalTrials.gov (NCT01091246) before enrollment began. Safety and noninferior immunogenicity of Q/LAIV were documented in adults before the start of this study. An independent safety monitoring committee was established before study onset.

All vaccines contained 10^{7.0±0.5} fluorescent focus units of each viral strain delivered as 0.1 mL into each nostril using a spray applicator. Four cold-adapted, temperature-sensitive, attenuated influenza strains were included in Q/LAIV: A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), B/Victoria (B/Malaysia/2506/2004) and B/Yamagata (B/Florida/4/2006). Manufacturing was the same as for commercial T/LAIV except that 4 strains were blended into the vaccine. T/LAIV preparations contained the same A strains plus a B strain from 1 of the lineages. The potencies of each strain were similar in each vaccine
Serious AEs and new onset chronic diseases were collected from the Registry for Regulatory Activities (www.meddramsso.com) version 12.0. Data for days 0–28 after each dose and were coded using the Medical Dictionary for Regulatory Activities (www.meddramsso.com) version 12.0. Serious AEs and new onset chronic diseases were collected from day 0 to day 180 after the final dose.

**Study Population and Sample Size Selection**

Target enrollment was 2300 subjects, with 500 subjects 9–17 years of age to receive a single dose and 1800 subjects 2–8 years of age to receive 2 doses approximately 1 month apart. The targeted sample size provides >92% power to demonstrate the immunologic noninferiority of Q/LAIV and >98% confidence to detect an adverse event (AE) that occurs at a rate of 0.3%. The power calculation for immunologic noninferiority was based on the t test and assumed 85% evaluable, a true GMT ratio ≤1.1, and a standard deviation of the natural logarithm-transformed antibody titer of 1.4 for each strain.

Subjects were randomized in a 3:1:1 ratio (Q/LAIV: T/LAIV containing a B strain of Yamagata lineage: T/LAIV containing a B strain of Victoria lineage) primarily to increase the number of subjects assessed for Q/LAIV safety. A central voice response system and blinded computer-generated allocation sequence were used to randomize (United BioSource Corporation, San Francisco, CA). Randomization was stratified by age (2–8 and 9–17 years) and, in subjects 2–8 years of age (2-dose group), by receipt of prior seasonal influenza vaccine. Subjects, investigators and sponsor staff responsible for assessment of safety were blinded until the end of the study; some sponsor staff were unblinded after all immunogenicity and 28-day postdose safety data were collected. Enrollment exclusions included immunodeficiency; chronic illness resulting in hospitalization in the previous year; change in medications or receipt of immunoglobulin or blood products in the previous 90 days; receipt of vaccines, investigational drugs, antiviral agents with activity against influenza or salicylates in the previous month; pregnancy or lactation; and active acute illness including fever. Subjects <2 years of age were excluded because T/LAIV is not indicated in that population based on existing safety data. Children with a history of asthma and children <5 years of age with recurrent wheezing were excluded to be consistent with US dosing recommendations for T/LAIV.

**Immunogenicity and Safety Assessments**

Blood samples for HAI antibody analysis were collected on day 0 before vaccination and approximately 1 month after dose 1 in all subjects except for those 2–8 years of age who had no history of prior seasonal influenza vaccination, who were sampled 1 month after dose 2 to comply with recommendations for T/LAIV dosing. HAI antibody titers (geometric mean of 2 replicates) were measured in the MedImmune Clinical Testing Laboratory (Mountain View, CA) and reported as the reciprocal of the last serum dilution that gave complete inhibition of hemagglutination. In the absence of HAI, the titer was reported as <4 with a value of 2 imputed for calculations. Seroconversion was defined as a 4-fold rise in HAI antibody from baseline in a seronegative subject, and seroresponse was a 4-fold rise in a subject who was not seronegative. Serosusceptible was defined as a baseline titer ≤8, and seronegative was defined as a baseline titer ≤4.

Solicited symptoms were collected daily during days 0–14 after each dose. Data for days 0–10 are presented to facilitate comparisons with existing data. Fever was defined as a temperature ≥38°C (100.4°F). Unsolicited AEs were collected during days 0–28 after each dose and were coded using the Medical Dictionary for Regulatory Activities (www.meddramsso.com) version 12.0. Serious AEs and new onset chronic diseases were collected from day 0 to day 180 after the final dose.

**Statistical Analyses**

HAI antibody results from both T/LAIV arms were combined for A/H1N1 and A/H3N2 strain analyses. For B strains, results from the Q/LAIV arm were compared with those from the T/LAIV arm containing the corresponding B strain. Noninferior immunogenicity was defined as having the upper bound of the 2-sided 95% confidence intervals (CIs) for the GMT ratio (T/LAIV divided by Q/LAIV) ≤1.5 for each strain. GMTs and geometric mean fold rises (GMFRs) were calculated as: GMT = \( \text{antilog} \left( \frac{\log \chi}{\log e} \right) \) and GMFR = \( \text{antilog} \left( \frac{\log y}{\log e} \right) \), where \( x \) is the postdose titer for each subject, \( y \) the fold rise in titer from baseline for each subject and \( e \) the natural logarithm. For the GMT or GMFR ratio, CIs were calculated using a percentile-based bootstrap method stratified by baseline serostatus. Test-based asymptotic 2-sided 95% CIs were calculated for the seroresponse rate difference (Q/LAIV − T/LAIV). For safety endpoints, Fisher exact P values were calculated for between-group comparisons of incidence rates. P values were used to screen for differences of potential significance at a 0.05 significance level; thus, no multiplicity adjustments were made. Missing data were excluded.

**RESULTS**

**Study Populations**

A total of 2312 subjects were randomized from March 29, 2010, to May 12, 2010. Follow-up was completed on December 27, 2010 (Fig. 1). Twenty-one subjects did not meet entry criteria for reasons not expected to impact immunogenicity; they were not excluded from analyses. Eight subjects received an incorrect first dose and were analyzed according to the treatment received. Subjects excluded from safety or immunogenicity populations before unblinding had not received study vaccine according to protocol, had no relevant safety data collected or had no HAI results for the correct immunogenicity time point. Subjects were analyzed according to the treatment received. Follow-up was similar in all study groups, and 97% of all subjects completed the study. In the 2-dose group, 40 (3.7%) subjects assigned to Q/LAIV and 23 (3.2%) assigned to T/LAIV did not receive dose 2, most commonly due to the inability to schedule within the dosing window. One T/LAIV and 1 Q/LAIV recipient were withdrawn from dosing by the parent due to AEs of vomiting with dizziness and gastroenteritis that the investigator considered unrelated to vaccine.

Study groups were well balanced for baseline characteristics (Table 1). The proportion of subjects in the immunogenicity population who were seronegative at baseline was similar in Q/LAIV and comparator groups: 35% and 37%, respectively, for A/H1N1, 28% and 28% for A/H3N2, 37% and 37% for B/Yamagata, and 37% and 36% for B/Victoria. The mean ± standard deviation number of days between dosing and blood sampling was similar in Q/LAIV (29.7±2.53) and T/LAIV (30.0±2.78) groups.

**Immunogenicity**

The GMT ratios with 95% CIs, representing the primary endpoint, and the GMFR ratios, which can account for differences in baseline titers, are shown in Figure 2. The upper bounds of all 95% CIs were ≤1.5; thus, noninferiority criteria were met for all strains. Although noninferior, the GMT and GMFR ratios were met for all strains. For B/Yamagata strain, 1.21 (95% CI: 1.07–1.37) and 1.13 (95% CI: 1.01–1.27), respectively, and the GMFR ratio for the A/H1N1 strain, 1.07 (95% CI 1.01–1.13), were statistically significantly different from 1. Data for the subset of subjects who were seronegative at baseline are also presented; CIs are wide because the sample size is small. The study was not powered for this endpoint.
The secondary endpoint of the proportion of all subjects and baseline seronegative subjects with seroconversion/seroresponse to each antigen is illustrated in Figure 3. The seroconversion rate to A/H3N2 was low in seronegative subjects regardless of the vaccine received. Seronegative subjects responded well to the B strains, with seroconversion occurring in 69%–83% of the Q/LAIV recipients. The only statistically significant difference in the by-strain proportion of subjects with 4-fold antibody rises was to the A/H1N1 strain in the serosusceptible subgroup, with 17.6% of T/LAIV subjects versus 12.7% of Q/LAIV subjects showing a seroresponse (95% CI for the rate difference: −9.7 to −0.4).

The demographic characteristics of subjects at enrollment are presented in Table 1. Data are for the intent-to-treat populations except that the number of subjects dosed includes all subjects as vaccinated, whether by randomization or by dosing error. T/LAIV-B/Victoria and T/LAIV-B/Yamagata indicate trivalent live attenuated influenza vaccines containing a B strain from the Victoria and Yamagata lineages, respectively. The data from both T/LAIV arms combined are presented.

FIGURE 1. Flow diagram of subjects enrolled at 97 sites in the United States. Data presented are from the intent-to-treat populations except that the number of subjects dosed includes all subjects as vaccinated, whether by randomization or by dosing error. T/LAIV-B/Victoria and T/LAIV-B/Yamagata indicate trivalent live attenuated influenza vaccines containing a B strain from the Victoria and Yamagata lineages, respectively.

### TABLE 1. Demographic Characteristics of Subjects at Enrollment (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Category</th>
<th>All Subjects</th>
<th>Subjects 2–8 Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q/LAIV (n = 1385)</td>
<td>T/LAIV* (n = 927)</td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>6.7 (3.8)</td>
<td>6.8 (3.8)</td>
</tr>
<tr>
<td>Gender, n (%) male</td>
<td>678 (49.0)</td>
<td>459 (49.4)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>303 (21.9)</td>
<td>201 (21.7)</td>
</tr>
<tr>
<td>Hispanic/Latino†</td>
<td>303 (21.9)</td>
<td>201 (21.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>971 (70.1)</td>
<td>669 (72.2)</td>
</tr>
<tr>
<td>White</td>
<td>250 (18.1)</td>
<td>166 (17.9)</td>
</tr>
<tr>
<td>Black</td>
<td>10 (0.7)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (0.5)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>2 (0.1)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>145 (10.5)</td>
<td>81 (8.7)</td>
</tr>
<tr>
<td>History of previous seasonal influenza vaccination, n (%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Data from both T/LAIV arms combined.
†Subjects of Hispanic/Latino ethnicity could be of any race.
NA indicates not applicable; Q/LAIV, quadrivalent live attenuated influenza vaccine; T/LAIV, trivalent live attenuated influenza vaccine.
For the secondary endpoint of achievement of a titer ≥32, responses were similar between comparators except that the proportion of subjects with a titer ≥32 to the B/Y amagata strain was statistically significantly lower in the Q/LAIV arm than in the T/LAIV arm (95% CI for the rate difference: −9.2 to −0.6). Differences were small (76% versus 82%), however, and the majority of subjects achieved a titer ≥32 to the Yamagata strain.

Cross-reacting immune responses to the heterologous B virus in subjects receiving T/LAIV were lower than responses to the homologous antigen (Fig. 3). Among seronegative subjects who received T/LAIV, 26% receiving B/Victoria responded with a 4-fold antibody rise to B/Yamagata compared with 85% of those who received B/Yamagata, and 24% of those receiving B/Yamagata responded with a 4-fold antibody response to B/Victoria compared with 74% of those who received B/Victoria. Antibody responses to influenza B virus strains are also illustrated by the reverse cumulative distribution curves of HAI antibody (Figure 4). The Q/LAIV vaccine containing both B antigens induced robust increases in antibody to B viruses from both lineages. In contrast, subjects who received T/LAIV containing a B strain from one lineage showed a greater increase in antibody to homologous virus and a lower response to heterologous virus.

Safety
Solicited symptoms were reported by similar proportions of subjects during days 0–10 after dosing, with the largest difference occurring in fever ≥38°C (100.4°F) (1.4% more Q/LAIV than T/LAIV recipients); none of the differences were statistically significant. Solicited symptoms occurring after the first dose in the subset of subjects who were 2–8 years of age are presented in Figure 5. In this age group, there was a small (2.0 percentage points) but statistically significant increase in fever ≥38°C (100.4°F) in the Q/LAIV group (5.1%) compared with the T/LAIV group (3.1%). In the T/LAIV group, more subjects who received a Yamagata strain had fever than did those who received a Victoria strain (Table 2). After the second vaccine dose in subjects 2–8 years of age, the proportion of subjects reporting any solicited symptom (Q/LAIV, 29%; T/LAIV, 28%) was lower than after the first dose.

AEs reported by all subjects during days 0–28 after dosing were also balanced, with 21% of subjects in each group reporting ≥1 AE after dose 1. Statistically significant differences were observed only for pyrexia (1.7% versus 0.7%, \( P = 0.04 \)), headache (0.9% versus 0.2%, \( P = 0.04 \)) and oropharyngeal pain (0.6% versus 0%, \( P = 0.03 \)) in Q/LAIV versus T/LAIV recipients, respectively, but
<2% of Q/LAIV subjects reported 1 of these events. The most common AE by frequency was vomiting (2.6% in the Q/LAIV arm and 2.2% in the T/LAIV group). In subjects 2–8 years of age who received 2 doses, fewer subjects had AEs after the second dose than after the first (Q/LAIV doses 1 and 2, 20% and 13%; T/LAIV 23% and 17%, respectively). In the group that received 2 doses, diarrhea was more frequent after dose 2 in the T/LAIV group than the Q/LAIV arm (P = 0.02). There were no life-threatening or fatal AEs.

Three subjects had a serious AE occurring within 28 days of any dose (all occurred after dose 2): appendicitis (Q/LAIV), Salmonella gastroenteritis with dehydration (Q/LAIV) and major depression (T/LAIV). During days 0–180 after the last dose, 6 (0.4%) and 5 (0.5%) subjects in the Q/LAIV and T/LAIV groups, respectively, reported a serious AE. None of these events was considered to be related to study dosing. New-onset chronic diseases were reported in 1.4% and 0.8% of subjects in the Q/LAIV and T/LAIV groups.

### TABLE 2. Number and Percent of Subjects Reporting Fever During Days 0–10 After Dose 1 in Subjects 2–8 Years of Age

<table>
<thead>
<tr>
<th>Fever</th>
<th>Q/LAIV, n (%)</th>
<th>T/LAIV, n (%)</th>
<th>T/LAIV-B/Yamagata, n (%)</th>
<th>T/LAIV-B/Victoria, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥38.0°C (100.4°F)</td>
<td>55 (5.1)†</td>
<td>22 (3.1)</td>
<td>15 (4.2)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>≥38.5°C (101.3°F)</td>
<td>31 (2.9)</td>
<td>10 (1.4)</td>
<td>4 (1.1)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>≥39.0°C (102.2°F)</td>
<td>13 (1.2)†</td>
<td>2 (0.3)</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>≥39.5°C (103.1°F)</td>
<td>4 (0.4)</td>
<td>1 (0.1)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

†P = 0.04, Q/LAIV vs. T/LAIV.

Q/LAIV indicates quadrivalent live attenuated influenza vaccine; T/LAIV, trivalent live attenuated influenza vaccine; T/LAIV-B/Yamagata, T/LAIV containing a B strain from the Yamagata lineage; T/LAIV-B/Victoria, T/LAIV containing a B strain from the Victoria lineage.

FIGURE 4. Reverse cumulative distribution curves of antibody to influenza B strains before and after dosing according to vaccine administered. HAI, hemagglutination inhibition; Q/LAIV, quadrivalent live attenuated influenza vaccine; T/LAIV, trivalent live attenuated influenza vaccine.

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respectively. There were no statistically significant differences between groups in serious AEs or new-onset chronic diseases by event type.

**DISCUSSION**

This study is the first to report the safety and immunogenicity of a quadrivalent, seasonal influenza vaccine in children. An Ann Arbor strain Q/LAIV, containing A/H1N1, A/H3N2, and 2 B strains, 1 from each B virus lineage, was shown to have immunogenicity and safety profiles comparable with those of a licensed, trivalent live influenza vaccine in children 2–17 years of age. The efficacy and safety profiles of this trivalent vaccine in children have been previously documented.20–22 In addition, Q/LAIV induced robust antibody titers to influenza B strains from both lineages, but the trivalent vaccines each induced robust antibody titers only to B strains from the homologous lineage. The use of Q/LAIV has the potential to provide important added protection in years when trivalent vaccines contain a B virus that is a lineage mismatch to the B strain that is responsible for most of the influenza B disease, which has occurred in 5 of the most recent 10 influenza seasons (2001–2002 to 2010–2011).23,24 Q/LAIV was immunogenic and met noninferiority criteria compared with T/LAIV. Although the Q/LAIV formulation was less immunogenic than T/LAIV for the B/Yamagata strain, the predetermined definition of noninferiority was met for all 4 strains. Lower immunogenicity for the B/Yamagata strain was also noted in the secondary endpoint of achievement of an HAI titer ≥32, an endpoint of uncertain relevance for live virus vaccines. This endpoint signifies a 50% protective level of antibody for inactivated influenza vaccines, which produce substantially higher titers of HAI antibodies, and for which the mechanism of action is primarily through the induction of antibody.27–30 This endpoint, established in adults, has recently been shown not to apply in children, even for inactivated vaccines.31 T/LAIV is thought to induce protective immunity through cell-mediated and mucosal immunologic responses, and the achievement of an HAI titer ≥32 is not required for protection.27,29,32–34 In addition, in the multiple comparisons assessed for secondary endpoints in the present study, the only other statistically significant difference was in the seroresponse rate to the A/H1N1 strain in the subset of subjects who were serosusceptible (titer ≤8) at baseline. Overall, the secondary endpoint data support the conclusion of the primary noninferiority endpoint.

One unexpected result of the present study was the low immunogenicity of the A/H3N2 component in T/LAIV and Q/LAIV compared with previous T/LAIV data.25,35–37 A/H3N2 (A/Uruguay/716/2007) hemagglutinin used in the present study was recommended by public health authorities and was used in commercial vaccines for the 2008–2009 and 2009–2010 influenza seasons. It contained an egg adaptation mutation that is associated with lower antibody response in ferrets.38 Selection of strains having sequences that enhance growth in eggs to maximize production but that do not modify antigenicity or immunogenicity may benefit live and inactivated influenza vaccine development. The A/H1N1 strain immunogenicity results were consistent with, although at the lower end of, responses for young children in previous studies of T/LAIV.23,35

The addition of a fourth vaccine strain did not result in clinically significant differences in the spectrum of safety events. In this study, some solicited symptoms, such as fever and nasal congestion, were less frequently observed in both study groups than in previous studies of T/LAIV.16,20–22 This suggests that the background rates of these events were lower in the present study, which was conducted outside the respiratory virus season. In data from a similar age group (2–6 years of age) enrolled in placebo-controlled studies of T/LAIV, nasal congestion occurred in half of the placebo recipients and 58% of T/LAIV recipients, and fever 38.5–38.9°C occurred in 4% of T/LAIV and 3% of placebo subjects.16

Much of the benefit of quadrivalent vaccine is expected to occur in children who, depending on patterns of wild-type circulation and on strains included in vaccines, might be susceptible to a B strain lineage due to lack of exposure despite the current recommendation and on strains included in vaccines, might be susceptible to a B strain lineage due to lack of exposure despite the current recommendation for universal vaccination in children 26 months of age.5-7 Influenza B causes disease in both children and adults, however, so that benefit is expected to occur in both populations.5,7,39-45 The safety of Ann Arbor strain Q/LAIV and the immunogenicity of the 2 B components suggest that the quadrivalent formulation may provide added benefit relative to the trivalent formulation by broadening the protection against type B influenza.

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