Safety of Live-Attenuated Influenza Vaccination in Cystic Fibrosis

AUTHORS: Constantina Boikos, MScPH, Gaston De Serres, MD, PhD, Lanny C. Landis, MD, PhD, François D. Boucher, MD, FRCP, Bruce Tapiéro, MD, FRCP, Patrick Daigleault, MD, FRCP, and Caroline Quach, MD, MSc, FRCP

*Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada; †Department of Social and Preventive Medicine, Laval University, Quebec City, Canada; ‡Institut national de santé publique du Québec, Quebec, Canada; Divisions of †Respiratory Medicine, and ‡Infectious Diseases, Department of Pediatrics, The Montreal Children’s Hospital, McGill University, Montreal, Canada; and ‡Infectious Diseases, and †Respiratory Medicine, Department of Pediatrics, Centre Mère-Enfant Soleil du CHU de Québec, Quebec, Canada; ‡Division of Infectious Diseases, Department of Pediatrics, CHU Sainte-Justine, Montreal, Canada; and †McGill University Health Centre, Vaccine Study Centre, Research Institute of the MUHC, Montreal, Canada

KEY WORDS
Cystic fibrosis, influenza, live-attenuated influenza virus vaccine, vaccine, childhood vaccination, vaccine safety

ABBREVIATIONS
AEFI—adverse events following immunization
CF—cystic fibrosis
CI—confidence interval
IRR—incidence rate ratio
LAIV—live attenuated influenza virus vaccine
RR—risk ratio
TIV—trivalent inactivated influenza vaccine

Ms Boikos carried out the statistical analyses and drafted the initial manuscript. Dr De Serres contributed to the study design, contributed to the interpretation of results and critically reviewed the manuscript. Dr Landis contributed to the study design, patient recruitment, and critically reviewed the manuscript. Drs Boucher, Tapiéro, and Daigleault contributed to patient recruitment and critically reviewed the manuscript. Dr Quach conceptualized and designed the study, carried out the initial statistical analyses, supervised the writing of the manuscript, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

doi:10.1542/peds.2014-0887
Accepted for publication Jun 25, 2014

Address correspondence to Caroline Quach, MD, MSc, FRCP, The Montreal Children’s Hospital, 2300 Tupper St, Montreal, QC H3H 1P3, Canada. E-mail: caroline.quach@mcgill.ca

(Continued on last page)

 WHAT’S KNOWN ON THIS SUBJECT: Influenza leads to respiratory deteriorations in cystic fibrosis (CF) patients. In children, live attenuated influenza virus vaccine (LAIV) is more efficacious than inactivated influenza vaccines, which could be beneficial for CF. Data on the safety of LAIV in this population are scarce.

 WHAT THIS STUDY ADDS: This study assesses LAIV’s safety in patients with CF and is necessary to determine whether the anticipated benefits associated with LAIV will outweigh potential risks. This can potentially lead to a recommendation for preferential LAIV use in this population.

abstract

OBJECTIVES: Given the improved efficacy of the nasal live-attenuated influenza virus vaccine (LAIV) compared with the injectable vaccine in children, we aimed to determine its safety in individuals with cystic fibrosis (CF).

METHODS: A cohort of 168 study participants, aged 2 to 18 years with CF, vaccinated with LAIV between October 1, 2012, and January 30, 2013, was followed prospectively for 56 days after initial vaccination in 3 pediatric CF clinics across the province of Quebec. Days 0 to 28 post-LAIV were considered the at-risk period for all outcomes of interest, and days 29 to 56 post-LAIV were considered the non–at-risk period. Incident respiratory deteriorations were defined as an unscheduled medical visit, hospitalization, or a new course of oral antibiotics for respiratory complaints. Using a self-controlled design, incidence rate ratios (IRR) were used to compare at-risk and non–at-risk periods.

RESULTS: Comparing at-risk to non–at-risk periods, there was no significant increase in the rate of incident respiratory deteriorations (IRR, 0.72; 95% confidence interval, 0.11–4.27) or all-cause hospitalizations (IRR, 1.16; 95% confidence interval, 0.30–4.81). A greater proportion of participants reported experiencing at least 1 minor respiratory and/or systemic adverse event after immunization during the at-risk period compared with the non–at-risk period (77% vs 54%, respectively). During the first week after LAIV, 13 of 188 (8%) children reported some wheezing, with the vast majority, 9 of 13 (69%), on the day of vaccination.

CONCLUSIONS: There was no increased risk of respiratory deterioration or all-cause hospitalization associated with LAIV in our study population. LAIV seems well tolerated in children and adolescents with CF. Pediatrics 2014;134:e983–e991
One in every 3600 Canadian children is born with cystic fibrosis (CF). CF is characterized by the dysfunction of the CF transmembrane regulator chloride channel and by abnormal inflammatory signaling, leading to excessive inflammatory responses, and impairment in the resolution of inflammation, leading to diminishing lung function and increased mortality. Infections with respiratory viruses (eg, influenza and rhinoviruses) are associated with exacerbation of pulmonary problems, disease progression, and increase in bacterial adherence in CF airways, which predisposes to secondary bacterial infection. Of all respiratory viruses, children with CF are affected for longer periods and more severely than healthy children. During the influenza pandemic, patients with CF had an increased morbidity and a higher case fatality compared with patients with other chronic respiratory diseases or to healthy control subjects. Of all respiratory viruses, influenza is, however, the only one that is currently vaccine-preventable.

In 2011 Flumist, a live-attenuated influenza virus vaccine (LAIV) administered by intranasal spray, was approved for use in Canada in individuals aged 2 to 59 years. The intranasal route of administration of LAIV directly stimulates mucosal immunity. Four trials in children and/or adolescents showed that LAIV reduced the risk of influenza by nearly half compared with the trivalent inactivated influenza vaccine (TIV). The Canadian National Advisory Committee on Immunization therefore recommended that LAIV be used preferentially for healthy children and adolescents and could also be used for children with chronic diseases. However, given CF’s increased inflammatory response and results from an earlier trial that reported an increased risk of wheezing after LAIV in asthmatic patients, there is a need to know if the greater efficacy of LAIV is outweighed by severe adverse events after immunization (AEFI) such as respiratory deteriorations.

Our primary objective was to determine LAIV’s safety in children and adolescents with CF by comparing incident respiratory deteriorations during at-risk and non–at-risk periods after immunization.

METHODS

Study Design and Patient Population

After obtaining informed consent, a cohort of children with CF aged 2 to 18 years vaccinated with LAIV through the regular process of care between October 1, 2012, and January 30, 2013, was followed prospectively for 56 days after the first dose of LAIV in 3 participating pediatric CF clinics across the province of Quebec. There was no concomitant vaccine administered.

Research nurses were responsible for participants’ recruitment and medical record review. Parents and participants completed a daily diary of symptoms for the 56 days after LAIV and recorded any treatments, medical consultations, or hospitalizations. Phone follow-up was done on days 1, 7, 14, 21, 28, 42, and 56 to collect data entered in diaries. Hospitalizations were also identified through CF clinic nurses and by review of medical records. The research ethics boards of the 3 participating hospitals approved this study.

Inclusion and Exclusion Criteria

Children on systemic corticosteroids, those with a medically attended wheezing episode in the 7 days before vaccination, patients <2 years of age, those with nasal polyps or rhinorrhea considered too significant (by the vaccinator) to allow LAIV to reach the nasal mucosa, and patients who were considered immunosuppressed were not eligible for LAIV vaccination and study inclusion but received TIV through the regular process of care. All patients who received TIV were excluded from the analyses.

Surveillance Period

Days 0 to 28 post-LAIV (29 days) were considered the at-risk period and days 29 to 56 (28 days) the non–at-risk period for all outcomes of interest. The same methodology was used to follow-up participants during the entire study.

Outcomes

The primary outcome was respiratory deteriorations resulting in either an unscheduled medical visit or a hospital admission. Secondary outcomes included incident oral antibiotic use for respiratory complaints, used as a proxy for respiratory deterioration, all-cause hospitalizations, and occurrence of respiratory (rhinorrhea and nasal congestion, cough, upper respiratory tract infection, bronchospasm, pharyngitis) and/or systemic adverse events (fever, malaise, headache, vomiting, abdominal pain) for the 56 days after LAIV administration. These symptoms are part of the standard assessment of serious adverse events of the Public Health Agency of Canada.

Statistical analysis

Analyses of primary and secondary outcomes were conducted using Poisson regression. AEFI rates were expressed as self-controlled incidence rate ratios (IRR) comparing incidence of outcomes during at-risk (days 0–28) and non–at-risk (days 29–56) periods. Because information on the exact duration of all-cause hospitalizations was not available, we subtracted 14 days for each hospitalization (as time not at risk) from the denominators of the IRRs. No time was subtracted from the denominators of the IRRs describing incident oral antibiotic use. We conducted an exploratory sensitivity analysis to compare the incidence of all-cause
hospitalizations using an analogous non–at-risk 28-day period in the preceding year (October 15–November 12, 2011).

Furthermore, we compared the proportion of reported symptoms experienced at least once in either study period using risk ratios (RRs) and 95% confidence intervals (CIs). These outcomes were stratified by age (<9 years and ≥9 years) based on current Canadian immunization guidelines13 that recommend 2 doses of influenza vaccine in the first year of vaccination in children aged <9 years and 1 dose of influenza vaccine in children ≥9 years, regardless of influenza vaccination history, because most will have an appropriate vaccine response to a single dose by this age. Outcomes were also stratified by use of inhaled antibiotics (marker for colonization with Pseudomonas aeruginosa) and azithromycin (used as a chronic antiinflammatory agent) at baseline. All statistical analyses were conducted by using Stata SE version 11.

RESULTS

Study Population

Overall, 185 of 377 (49%) children with CF followed in the 3 participating clinics were recruited: 54 of 77 (70%) patients from the Montreal Children’s Hospital; 57 of 180 (32%) from the CHU Sainte-Justine; and 74 of 120 (62%) from the CHU de Québec. Of the 185 recruited participants, 17 received a dose of TIV in their local public health clinic and were subsequently excluded from the analyses. There was no loss to follow-up. In total, 4872 person-days at risk and 4704 person-days non–at-risk were recorded. Only 2 of 168 participants needed and received a second dose of LAIV from their CF clinic. Study participants’ baseline characteristics are described in Table 1. Sixty subjects (35.7%) were <9 years of age. At baseline, 18.5% (31 of 168) of study participants used inhaled antibiotics, 5.0% (5 of 168) used oral azithromycin, and 37.5% (63 of 168) were taking inhaled and/or nasal corticosteroids.

Primary and Secondary Outcomes

Primary Outcome

There was no significant difference in the rate of incident respiratory deteriorations or all-cause hospitalizations during the at-risk period compared with the non–at-risk period. Seven respiratory deteriorations were reported, all requiring hospitalization: 3 in the at-risk (days 0, 7, 26) and 4 in the non–at-risk period (days 35, 41, 42, 50; IRR 0.72; 95% CI 0.11–4.27). Influenza virus was not detected in any case of respiratory deterioration. Figure 1 details dates of vaccination and influenza activity in the province.

Secondary Outcomes

Two oral antibiotic treatments were initiated during the at-risk period, compared with 6 during the non–at-risk period for respiratory complaints (IRR 0.32; 95% CI 0.05–1.80). Eleven all-cause hospitalizations occurred: 6 during the at-risk and 5 in the non–at-risk period, (IRR 1.16; 95% CI 0.30–4.81). Details on reasons for hospitalizations and antimicrobial prescriptions are given in Table 2. For the same cohort of patients, 5 all-cause hospitalizations were recorded for the 28-day sensitivity analysis control period in the previous year (IRR 1.16).

Reported Solicited Symptoms

The proportion of solicited symptoms reported during the at-risk and non–at-risk periods are detailed in Table 3. Overall, 64% of participants (107 of 168) experienced at least 1 solicited symptom in the first week after vaccination. Except for respiratory deteriorations, none of the reported solicited symptoms required hospitalization. Only 1 participant had an unscheduled medical visit for joint pain that started

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age (y)</th>
<th>Mean age (SD)</th>
<th>Median age</th>
<th>Age range</th>
<th>Age &lt;9 (n, %)</th>
<th>2–4</th>
<th>5–8</th>
<th>Male</th>
<th>83 (49.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race or ethnic group</td>
<td>Caucasian</td>
<td>161 (96.4%)</td>
<td>Black</td>
<td>4 (2.4%)</td>
<td>Asian</td>
<td>2 (1.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received TIV</td>
<td>All</td>
<td>60 (35.7)</td>
<td>Not in past 2 y</td>
<td>110/166</td>
<td>In the previous 2 y</td>
<td>17/166</td>
<td>Last year</td>
<td>8/166</td>
<td>Two years ago</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>Inhaled antibiotics</td>
<td>31 (18.5)</td>
<td>Azithromycin</td>
<td>5 (3.0)</td>
<td>Corticosteroid use</td>
<td>30 (17.7)</td>
<td>Nasal</td>
<td>19 (11.3)</td>
<td>Both</td>
</tr>
</tbody>
</table>
| TABLE 1 Baseline Characteristics of Study Participants (n = 168)

- Race/ethnicity information missing for 1 of 168 study participants.
- Includes Caucasian and Middle Eastern/Arabic, Caucasian and Black, and Caucasian and Latin American.
- Seasonal influenza vaccination history not available for 2 of 168 study participants.
- At time of vaccination.
- Colimycin, tobramycin, amikacine, Cayston.
8 days after vaccination. The largest magnitude RRs were for joint pain (RR 10.50; 95% CI 2.50–44.08), muscle aches (RR 9.67; 95% CI 3.00–31.12), and vomiting (RR 7.67; 95% CI 2.35–25.05). Fifty-nine (35%) patients had onset of fever during the first 6 days after vaccination (Fig 2, Table 3), and the greatest number of febrile children was observed on day 4 postvaccination (n = 42, 25%), with a maximal temperature of 39.6°C. The majority of febrile episodes (58 of 92; 55%) lasted only 1 day. During the at-risk period, participants aged <9 years were more likely to experience runny nose and vomiting compared with participants aged ≥9 years. Thirteen of 15 participants who reported redness in both eyes did so during the first 3 days after LAIV. Ten participants reported facial swelling during the first 3 days after LAIV.

Wheezeing was more likely to be reported during the at-risk period (RR 4.33; 95% CI 1.26–14.93), with the highest reported incidence (9 of 168) on the day of vaccination (Fig 3). None of the participants who reported wheezing on day 0 reported wheezing on any other day during the study period; 7% (13 of 168) of participants reported wheezing at least once during days 0 to 6 after vaccination with LAIV, and no wheezing was reported beyond the first week after LAIV during the at-risk period. There were no statistically significant differences between those who reported and did not report wheezing during the at-risk period. The RR of wheezing in those on and not on inhaled corticosteroids was 0.23 (95% CI 0.03–1.75; Table 4). Only 2 study participants had a history of allergic bronchopulmonary aspergillosis (ABPA), a common cause of wheezing in patients with CF.24 One participant was receiving antifungal treatment at the time of vaccination, and we had no information on ABPA treatment of the other.

Regardless of inhaled corticosteroid use at baseline, there was a similar increased risk of worsening of cough during the at-risk period compared with the non–at-risk period: RR 1.38; 95% CI 0.61–3.09 for participants on inhaled and RR 2.00; 95% CI 1.11–3.61 for participants not on inhaled corticosteroids. Of note, only patients with CF who have comorbid asthma and/or airway hyperreactivity are generally prescribed inhaled corticosteroids. Nasal corticosteroids use at baseline seemed to modify the risk of runny nose (RR 1.11; 95% CI 0.51–2.42 for participants on nasal corticosteroids versus RR 3.37; 95% CI 2.15–5.29 for participants not on nasal corticosteroids) and nasal congestion (RR 1.63; 95% CI 0.76–3.45 for participants on nasal corticosteroids versus RR 3.6; 95% CI 2.14–6.04 for participants not on nasal corticosteroids) during the at-risk compared with the non–at-risk period. Similarly, in days 0 to 6 post-LAIV, there was a decreased risk of runny nose (RR 0.68; 95% CI 0.37–1.25) and nasal congestion (RR 0.71; 95% CI 0.36–1.38) in children taking versus not taking nasal corticosteroids at baseline.

DISCUSSION

Previous clinical trials and observational studies did not explore the safety of LAIV in a pediatric population with CF.
In our pediatric population with CF, there was no increased incidence of respiratory deteriorations and all-cause hospitalizations when comparing the at-risk and non–at-risk periods. None of the hospitalizations were considered associated with LAIV vaccination. Two participants were prescribed antibiotics during the at-risk period representing 1.2% over a 1-month period. Our results are much lower compared with proportions previously reported (40% of participants needing antimicrobial agents over a 6-month period, or 6.7% per month).\(^\text{17}\)

A greater proportion of study participants reported experiencing an AEFI during the at-risk period compared with the non–at-risk period, with the majority reporting symptoms in the week after vaccination. In our population, 64% of participants reported at least 1 symptom in the first week after vaccination, with the overwhelming majority not needing medical attention. This proportion is similar to that reported after TIV: 15 of 21 (71%) participants with CF vaccinated with TIV reported at least 1 systemic AEFI in the 5 days after vaccination.\(^\text{25}\)

Participants on nasal corticosteroids seemed to have a lower risk of developing a runny nose and nasal congestion after LAIV. However, given our small sample size, the CIs around the RRs for participants on and those not on nasal corticosteroids at baseline were not statistically significantly different. Inhaled corticosteroids at baseline did not modify the risk of AEFI and were a particularly important factor to analyze because their use is a contraindication to LAIV vaccination in most jurisdictions.\(^\text{26}\)

Participants reported more wheezing during the at-risk period, mainly on the day of vaccination. There was no episode of wheezing beyond the first week after LAIV, and these episodes did not lead to unscheduled visit, hospitalization, or prescription of oral antimicrobial agents. We did not have information on non–medically attended wheezing episodes that occurred before vaccination; some episodes of wheezing occurring on day 0 may have therefore been prevalent rather than incident. We know, however, that none of the included participants had a medically attended visit for wheezing in the 7

### TABLE 2 Hospitalizations and Incident Oral Antibiotic Use

<table>
<thead>
<tr>
<th>Reason for Admission/Antibiotic Name</th>
<th>Date of Event</th>
<th>Days After LAIV Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV antibiotics for <em>B. cepacia</em> in sputum collected a month earlier</td>
<td>November 6, 2012</td>
<td>0</td>
</tr>
<tr>
<td>Intestinal obstruction: meconium ileus equivalent (partial occlusion of small bowel)</td>
<td>November 13, 2012</td>
<td>0</td>
</tr>
<tr>
<td>Scheduled hospitalization for FEV₁ decrease</td>
<td>November 2, 2012</td>
<td>3</td>
</tr>
<tr>
<td>Distal intestinal occlusion</td>
<td>December 5, 2012</td>
<td>13</td>
</tr>
<tr>
<td>Progressive respiratory deterioration evolving during the last year, resulting in hospitalization for IV treatment, with significant decrease in pulmonary function tests</td>
<td>December 13, 2012</td>
<td>16</td>
</tr>
<tr>
<td>Elective admission to hospital for IV antibiotics</td>
<td>November 19, 2012</td>
<td>29</td>
</tr>
<tr>
<td>Intestinal subocclusion</td>
<td>December 8, 2012</td>
<td>30</td>
</tr>
<tr>
<td>Scheduled hospitalization for replacement of nonfunctional port-a-cath, followed by bronchial superinfection</td>
<td>December 18, 2012</td>
<td>35</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> positive bronchial lavage and sinus infection with <em>Pseudomonas</em></td>
<td>November 28, 2012</td>
<td>41</td>
</tr>
<tr>
<td>Pulmonary superinfection</td>
<td>January 15, 2013</td>
<td>42</td>
</tr>
<tr>
<td>Respiratory deterioration</td>
<td>December 27, 2012</td>
<td>50</td>
</tr>
<tr>
<td>Respiratory deterioration</td>
<td>October 21, 2011</td>
<td></td>
</tr>
<tr>
<td>Respiratory deterioration</td>
<td>October 31, 2011</td>
<td>—</td>
</tr>
<tr>
<td>Attention-deficit disorder and adverse event from medication</td>
<td>October 18, 2011</td>
<td>—</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> superinfection</td>
<td>November 29, 2012</td>
<td>—</td>
</tr>
<tr>
<td>Pulmonary deterioration</td>
<td>November 2, 2011</td>
<td>—</td>
</tr>
<tr>
<td>Antibiotics prescribed (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>December 18, 2012</td>
<td>14</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>November 28, 2012</td>
<td>14</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>December 14, 2012</td>
<td>30</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>November 18, 2012</td>
<td>33</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>December 3, 2012</td>
<td>35</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>December 13, 2012</td>
<td>36</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>December 16, 2012</td>
<td>38</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>December 26, 2012</td>
<td>42</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second; IV, intravenous.
days before vaccination. Similar to our study results, Gaglani et al found that LAIV administration was not associated with an increased risk of medically attended acute respiratory illnesses in healthy children aged 17 to 20 months old at enrollment who had a history of intermittent wheezing.27

In our study cohort, 9% of participants reported redness in both eyes and difficulty breathing; 6% reported facial swelling. Most of these symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All Study Participants (n = 168)</th>
<th>Days 0–28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days 0–6</td>
<td>Days 0–28</td>
</tr>
<tr>
<td>Runny nose</td>
<td>56 (33%)</td>
<td>74 (44%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>48 (29%)</td>
<td>67 (40%)</td>
</tr>
<tr>
<td>Headache</td>
<td>48 (29%)</td>
<td>56 (33%)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>46 (27%)</td>
<td>53 (32%)</td>
</tr>
<tr>
<td>Worsening of cough</td>
<td>18 (11%)</td>
<td>33 (20%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>36 (21%)</td>
<td>49 (29%)</td>
</tr>
<tr>
<td>Increased sputum</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27 (16%)</td>
<td>34 (20%)</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>23 (14%)</td>
<td>29 (17%)</td>
</tr>
<tr>
<td>Chills</td>
<td>24 (14%)</td>
<td>28 (15%)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>17 (10%)</td>
<td>23 (14%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (10%)</td>
<td>22 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (13%)</td>
<td>22 (13%)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>17 (10%)</td>
<td>21 (13%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (11%)</td>
<td>23 (14%)</td>
</tr>
<tr>
<td>Redness in both eyes</td>
<td>15 (9%)</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>15 (9%)</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>17 (10%)</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>13 (8%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Facial swelling</td>
<td>10 (6%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Fever</td>
<td>59 (35%)</td>
<td>64 (38%)</td>
</tr>
<tr>
<td>At least 1 symptom</td>
<td>107 (64%)</td>
<td>130 (77%)</td>
</tr>
</tbody>
</table>

Number of participants reporting redness in both eyes: 9 on day 0, 3 on day 1, 1 on each day 3, 4, and 6; 9 participants reported facial swelling on day 0 and 1 on day 3.

a Symptom dichotomized as ever/never experience during at-risk and non-at-risk periods.

b Comparing at-risk versus non-at-risk periods

FIGURE 2
Number of Febrile Children per Study Day. Note: fifty-eight episodes of 1-day fever, 20 episodes of 2-day, 7 episodes of 3-day, 2 episodes of 4-day, 3 episodes of 5-day, and 2 episodes of 6-day fever.
occurred within 24 hours of vaccination and are compatible with oculorespiratory syndrome, as previously reported after TIV. An observational study of infants and toddlers vaccinated with TIV from the provinces of Quebec and British Columbia reported that 6% (18 of 320) and 0.8% (3 of 370) of participants from Quebec and British Columbia, respectively, had at least 1 symptom compatible with oculorespiratory syndrome in the 72 hours after vaccination, which was mainly cough (both prevalent and incident) and reported more often in Quebec.

Our study has 3 main limitations. First, it is possible that our results are biased by time-varying effects such as changes in medications used and disease severity. This is particularly relevant for the effect estimate obtained from the sensitivity analysis where individuals are compared with themselves a year before study enrollment. Moreover, there was increased circulation of influenza A/H3N2 in December 2012, which can bias our results. In our cohort, 14% of participants had been vaccinated before November 1 and 80% before December 1, which meant that a variable but significant proportion of our patient-days considered non-at-risk occurred while influenza was circulating. However, because LAIV is more effective than TIV, we expect that our study participants were protected by the time influenza was circulating. None of the patients admitted tested positive for influenza, and no course of antimicrobial agents was initiated during the non-at-risk period. Additionally, our study results may be affected by the “healthy vaccine effect,” a form of selection bias in which only subjects who are healthy at the time of vaccination, are vaccinated, leading to a subsequent decrease in risk of adverse outcomes in the immediate period after vaccination.

### TABLE 4 Baseline Characteristics of Participants Who Reported Wheezing During the At-Risk Period

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Wheezing (n = 13)</th>
<th>No Wheezing (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>7 (54%)</td>
<td>78 (50%)</td>
</tr>
<tr>
<td>Age (y):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>9.39 (4.44)</td>
<td>10.7 (4.76)</td>
</tr>
<tr>
<td>Median age</td>
<td>9.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Age range</td>
<td>2.7–16.6</td>
<td>1.9–18.1</td>
</tr>
<tr>
<td>Age &lt;9 y, n (%)</td>
<td>6 (46%)</td>
<td>54 (35%)</td>
</tr>
<tr>
<td>Corticosteroid use at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled only</td>
<td>1 (8%)</td>
<td>25 (16%), <em>P = .89</em></td>
</tr>
<tr>
<td>Nasal only</td>
<td>1 (8%)</td>
<td>18 (12%), <em>P = .1</em></td>
</tr>
<tr>
<td>Both</td>
<td>0</td>
<td>18 (12%), <em>P = .36</em></td>
</tr>
<tr>
<td>Antibiotic use at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled</td>
<td>3 (23%)</td>
<td>28 (18%)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Vaccination history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last year only</td>
<td>0</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Two years ago only</td>
<td>1 (8%)</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Previous 2 y</td>
<td>11 (85%)</td>
<td>99 (65%)</td>
</tr>
<tr>
<td>Not in past 2 y</td>
<td>1 (8%)</td>
<td>30 (20%)</td>
</tr>
</tbody>
</table>

Reported wheezing at least once during at-risk period.

* Percentages may not add to 100% due to rounding.

Seasonal influenza vaccination history not available for 2 study participants.

* *P* value for 2-sided Fisher’s exact test comparing wheezing and no wheezing among corticosteroid takers (inhaled, nasal, or both) during the at-risk period.

### FIGURE 3

Reported incident wheezing episodes by study day. Note: during the at-risk period, there were 11 episodes of 1-day and 2 episodes of 3-day wheezing. During the non-at-risk period, there were 2 episodes of 9-day wheezing and 1 episode of 7-day wheezing.
vaccination as the index date of exposure can overcome this bias; however, participants were vaccinated through the regular process of care and were thus not allocated an a priori vaccination date. Moreover, although measurement error may be present in primary and secondary outcomes, we relied on hospital records rather than self-reported hospitalizations and respiratory deteriorations to minimize such bias. Finally, the study was not powered to detect significant effects of LAIV on adverse outcome in subgroups (stratified by age and corticosteroid use).

Our study has several integral strengths. First, patients with CF have key time-invariant characteristics related to prognosis that make interpatient comparability difficult and complicated to control for. Therefore, as children act as their own controls, time-invariant confounders (eg, gender, genetic makeup, overall health) are implicitly controlled for by design,\textsuperscript{30,32} minimizing the risk of residual confounding.\textsuperscript{22,33} Second, there was no loss to follow-up, and almost half of the patient population with CF from these 3 specialized clinics was recruited in the study. More than 70% of children with CF in Quebec are followed in 1 of the 3 CF clinics participating in this study. We are thus confident that our sample is representative of children with CF in the province of Quebec. Third, a sensitivity analysis at a time when children with CF were not vaccinated with LAIV was conducted giving similar results, ensuring that the 4-week control period chosen did not bias our analysis away from the null because the onset of influenza season in 2012–2013 was earlier than usual. Finally, the amount of person-time excluded for respiratory deterioration and intestinal occlusion-related hospitalization is most likely overestimated, thus overestimating the IRR presented.

CONCLUSIONS

Overall, although we identified an increased risk of AEFI after LAIV vaccination, in particular an increase in wheezing, we did not find an increased risk of respiratory deterioration associated with LAIV in our study population. Given the clinically severe impact of influenza infection in a child with CF, as well as LAIV’s improved efficacy over TIV, particularly in young children, the risks associated with infection outweigh the risk of minor respiratory and systemic symptoms associated with the vaccine. The intranasal route of administration could make this vaccine more acceptable to a patient population that needs to be vaccinated yearly, potentially increasing vaccination acceptance and coverage. Because LAIV seems well tolerated in children and adolescents with CF, a population in whom the risk of adverse events after LAIV is the highest, LAIV use in other pediatric populations with chronic conditions (not immunosuppressed) should be further studied.

ACKNOWLEDGMENTS

We thank the research nurses and coordinators, as well as the CF clinic personnel and patients for their support in this study. We are thankful to Dr Jacques E. Marcotte for his support and help on this study.

REFERENCES


23. The 2011 Annual Canadian Cystic Fibrosis Registry. Toronto, Canada: Cystic Fibrosis Canada; 2011


(Continued from first page)

FINANCIAL DISCLOSURE: C. Quach has received research funding from AbbVie, GlaxoSmithKline, Pfizer, and Sage for unrelated studies. G. De Serres has received research funding from GlaxoSmithKline and Sanofi Pasteur and received reimbursement for travel fee to attend a GSK ad hoc Advisory board meeting. B. Tapiéro has received research funding from Novartis and Sanofi Pasteur for unrelated studies. L.C. Lands has received funds to attend a Novartis Advisory board meeting. P. Daigneauit has given conferences through unrestricted funding by Novartis and Takeda. The other authors have no financial relationships relevant to this article to disclose.

FUNDING: Funding for this study was provided by the Quebec Ministry of Health (Ministère de la santé et des services sociaux). The Quebec Ministry of Health had no input in the study design, data analysis or the manuscript. Constantina Boikos is supported through a Public Health Agency of Canada (PHAC), Canadian Institutes of Health Research (CIHR) - PHAC/CIHR Influenza Research Network (PCRIN) trainee award.

POTENTIAL CONFLICTS OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
An error occurred in the article by Boikos et al, titled “Safety of Live-Attenuated Influenza Vaccination in Cystic Fibrosis” published in the October 2014 issue of Pediatrics (2014;134(4):e983–991; doi 10.1542/peds.2014-0887). On page e998, the authors inadvertently counted incorrect numbers of study participants reporting the following adverse events following immunization in Table 3: headache, worsening of cough, increased sputum, abdominal pain, muscle aches, nausea, vomiting, eye redness, difficulty breathing and difficulty swallowing. These miscalculations were due to coding errors and were discovered in the course of conducting a secondary analysis using the same data. The major conclusions of the paper remain unchanged and the sub-analyses pertaining to the adverse events following immunization of wheezing and fever are also the same. Furthermore, these corrections do not change any major conclusions reported in this study. The analyses have been re-run and the corrected version of Table 3 is below. The two largest risk ratios now correspond to difficulty breathing and to redness in both eyes, not joint pain and muscle aches as previously reported. The overall risk of reporting at least one minor symptom during follow up is 2.28 times (95% CI 1.87, 2.78) higher in the first month following live-attenuated influenza vaccination compared with the second month, not 1.43 (95% CI 1.22-1.68) as previously reported.

doi:10.1542/peds.2016-2521

TABLE 3  
Reported Symptoms by Study Period and Age

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All Study Participants (n = 168)</th>
<th>Days 0-28</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days 0-6</td>
<td>Days 0-28</td>
<td>Days 29-56</td>
</tr>
<tr>
<td>Runny Nose</td>
<td>56 (33%)</td>
<td>74 (44%)</td>
<td>28 (17%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>48 (29%)</td>
<td>67 (40%)</td>
<td>23 (14%)</td>
</tr>
<tr>
<td>Headache</td>
<td>42 (25%)</td>
<td>62 (38%)</td>
<td>14 (8%)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>46 (27%)</td>
<td>65 (40%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Worsening of cough</td>
<td>28 (17%)</td>
<td>48 (29%)</td>
<td>17 (11%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>26 (16%)</td>
<td>49 (29%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Increased sputum</td>
<td>29 (17%)</td>
<td>33 (20%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28 (17%)</td>
<td>34 (20%)</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>24 (14%)</td>
<td>29 (17%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Chills</td>
<td>24 (14%)</td>
<td>26 (15%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>17 (10%)</td>
<td>23 (14%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (10%)</td>
<td>22 (13%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (13%)</td>
<td>22 (13%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>17 (10%)</td>
<td>21 (13%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (9%)</td>
<td>22 (13%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Redness in both eyes</td>
<td>14 (8%)</td>
<td>15 (9%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>17 (10%)</td>
<td>18 (11%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>13 (8%)</td>
<td>16 (10%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>13 (8%)</td>
<td>13 (8%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Facial swelling</td>
<td>10 (6%)</td>
<td>10 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>59 (35%)</td>
<td>64 (38%)</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>At least 1 symptom</td>
<td>127 (76%)</td>
<td>148 (88%)</td>
<td>65 (39%)</td>
</tr>
</tbody>
</table>

a Symptom dichotomized as ever/never experience during at-risk and non-at-risk periods.

b Comparing at-risk versus non-at-risk periods.

Number of participants reporting redness in both eyes: 9 on day 0, 2 on day 1, 1 on each day 3, 4, and 6. Also, 9 participants reported facial swelling on day 0 and 1 on day 3.
Safety of Live-Attenuated Influenza Vaccination in Cystic Fibrosis
Constantina Boikos, Gaston De Serres, Larry C. Lands, François D. Boucher, Bruce Tapiéro, Patrick Daigneault and Caroline Quach

Pediatrics; originally published online September 15, 2014;
DOI: 10.1542/peds.2014-0887

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/early/2014/09/09/peds.2014-0887