Recurrence Risk of Oculorespiratory Syndrome After Influenza Vaccination

Randomized Controlled Trial of Previously Affected Persons

Gaston De Serres, MD, PhD; Danuta M. Skowronski, MD, FRCP; Maryse Guay, MD, FRCP; Louis Rochette, MSc; Karen Jacobsen, BEd; Theresa Fuller, CRC; Bernard Duval, MD, FRCP

Background: Oculorespiratory syndrome (ORS) after influenza vaccination has many features of an allergic reaction.

Methods: The objective of the study was to estimate the recurrence rate of ORS after receipt of either of 2 influenza vaccines available in Canada for the 2002-2003 influenza season in individuals who experienced ORS in 2000 or 2001. We designed a randomized, crossover, double-blind, placebo-controlled trial in which patients received the vaccine and the placebo 7 days apart. Patients were contacted by telephone at 24 hours and seen at 7 days to collect information about the recurrence of ORS symptoms. The 146 patients belonged to 3 groups: group A (46 patients) had ORS in 2000 but were not revaccinated in 2001, group B (50 patients) had ORS in 2000 and were revaccinated in 2001, and group C (50 patients) had ORS in 2001 but not in 2000. Half of the participants received Fluviral S/F (Shire Biologics) and half received Vaxigrip (Aventis Pasteur). The main outcome measure was the risk difference in ORS symptoms in the 24 hours after receiving the vaccine and after receiving placebo.

Results: Recurrence attributable to the vaccine occurred in 34% (95% confidence interval, 21%-47%) of patients after receiving Fluviral S/F and in 15% (95% confidence interval, 2%-28%) after receiving Vaxigrip. The rate was twice as high in group A vs groups B and C. The risk of ORS was highest and most significant in group A patients vaccinated with Fluviral S/F. Most cases were mild, with 94% of patients with recurrence indicating that they would still be revaccinated the next year.

Conclusions: Despite high recurrence rates, revaccination of persons previously affected by ORS seems to be safe. Oculorespiratory syndrome is not anaphylactic, and most recurrences are benign. Most patients remain willing to be revaccinated.

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European countries where this vaccine is largely distributed. Finally, a recent investigation in the United States identified more than 2000 cases fitting the ORS case definition reported during the past 10 years to the Vaccine Adverse Events Reporting System.

A recent clinical trial looked at the safety of revaccination of patients who had ORS in 2000-2001 with the reformulated 2001-2002 Fluviral S/F. However, the study was aborted according to protocol when the vaccine-attributable risk of ORS exceeded 10%. When the study was terminated, 61 individuals had received a single dose of either vaccine (n = 34) or placebo (n = 27). The estimate of the vaccine-attributable recurrence risk of ORS was 27% to 33% according to the ORS case definition. In contrast to the high recurrence rates observed in these clinical trials, telephone surveys in Quebec and British Columbia found that approximately one third of patients who sustained ORS in 2000 had been revaccinated and that 5% to 8% reported a recurrence.10,11

The objective of the present study is to estimate the recurrence rate of ORS in individuals previously affected in 2000 or 2001 for each of the 2 influenza vaccines available in Canada for the 2002-2003 influenza season.

METHODS

For this placebo-controlled crossover design clinical trial, patients were recruited in Vancouver, Quebec City, and the Montréal area (southeast of Montreal). Three groups of patients 18 years and older were recruited: group A included patients who had ORS in 2000-2001 and were not revaccinated against influenza, group B included patients who had ORS in 2000-2001 and were revaccinated in 2001-2002, and group C included patients who had a first occurrence of ORS in 2001-2002. Exclusion criteria selected outpatients who were already vaccinated, those who could not be present for the 2-week follow-up, and those who at the time of immunization during this trial had conditions that, in the opinion of the site investigator, would hamper the recognition of ORS-like symptoms (red eyes and chest conditions) in the postimmunization period, such as conjunctivitis, allergies that cause eye irritation, and chronic symptomatic respiratory disease. Participants were unpaid patients recruited from the list of ORS cases reported to public health units.

Each patient received the placebo and the vaccine 7 days apart. Half of the participants of each of the 3 groups were randomly allocated to receive Fluviral S/F, and Vaxigrip was given to the other half. Randomization was done separately for each of the 3 groups and for each site. To minimize the likelihood of unbalanced groups, participants were randomized in blocks of 4 to receive Fluviral S/F–placebo, Vaxigrip–placebo, Fluviral S/F, or placebo-Vaxigrip, with the order of each sequence also being randomized from block to block.

VACCINES, PLACEBO, AND Masking

Fluviral S/F contained 15 µg per 0.5-mL dose of hemagglutinin antigen of each of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Victoria/504/2000, whereas the Vaxigrip strains were A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Johannesburg/5/99. The reformulated Fluviral S/F vaccine for 2002-2003 included sodium deoxycholate and Triton X-100 as splitting agents, whereas Vaxigrip included only Triton X-100. Residual amounts of these splitting agents would have been present in the final products. Isotonic sodium chloride solution was used as the placebo. Masking was achieved by having a designated research nurse at each site draw up the assigned solutions in a conventional plastic syringe with an opalescent barrel wall. Another nurse double-checked the assignment and the product before the syringe was handed to the immunizing nurse, who, along with the patient, was masked to its content.

DATA COLLECTION

On day 0, after enrollment and acquisition of informed consent, the nurse collected demographic data and the baseline medical history and administered the first injection. All participants were given a diary in which to record any solicited and unsolicited symptoms that developed during the 7 days after immunization and any medications taken to relieve symptoms during that time. On day 1, patients were contacted by telephone by a trained nurse, who systematically collected data on ORS symptoms that occurred during the first 24 hours. Participants who had ORS symptoms were again contacted by telephone on day 3 to obtain data on the evolution of symptoms. Approximately 1 week after the first injection, patients had a second visit, during which follow-up data regarding adverse events (per the patient diary spanning days 1–7) were collected and the second injection was given. The follow-up sequence was similar to that after the first injection except for data collection of adverse events between days 2 and 7 after the second injection, which was done by telephone.

ORS CASE DEFINITION

For the primary analysis, ORS was defined according to the National Advisory Committee on Immunization 2001 case definition as at least 1 ORS symptom (bilateral red eyes, sore throat, difficulty swallowing, cough, breathing difficulty, chest tightness, wheezing, and facial or palpebral edema) with onset within 24 hours of influenza vaccination, with no time limit for resolution of symptoms. In secondary analyses, more stringent definitions requiring either 2 or more ORS symptoms or a combination of 2 symptom categories (edema, ocular, and respiratory) were used. In the ocular symptom category, we included ocular pain or pruritus, a symptom that was not included in the ORS defining list of symptoms but that was found to be as significant and frequent as red eyes in previous ORS clinical trials. The severity of ORS was categorized in relation to the effect on activities of daily living, including sleep, as follows: (1) present but not bothersome, with no effect on daily activities; (2) bothersome and interferes with daily activities without preventing them; and (3) distressing and prevents daily activities (eg, unable to work or sleep or carry out activities of daily living).

The protocol was approved by the ethics boards of each of the 3 sites.

SAMPLE SIZE

The sample size was calculated based on a previous study, in which ORS occurred in 31% of participants after receiving the vaccine and in 6% after receiving placebo. To detect such a difference with a 5% significance level and 80% power in a matched analysis, 37 participants were required. Because the risk of recurrence was 1.5 to 1.9 times higher with Fluviral S/F than with Vaxigrip, for the latter, 78 to 130 participants were required. Given the limited number of potential participants that could be enrolled and the requirement from the sponsor to explore the risk of ORS in patients who had ORS in 2000 or 2001, it
was decided to recruit 75 patients for each vaccine and to divide them equally among the 3 groups (A, B, and C).

STATISTICAL ANALYSIS

The primary outcome of the study is the risk of ORS attributable to each vaccine estimated in matched analysis as the risk difference in the cumulative incidence of ORS after receiving vaccine and after receiving placebo using generalized estimating equations.13

RESULTS

Of the 406 potential participants successfully contacted, 125 (31%) were not eligible. Of the 281 eligible patients, 150 (53%) agreed to participate, and 146 received the injections according to protocol. Two participants were excluded because they were given the injection while already displaying ORS-defining symptoms. Another excluded participant developed labyrinthitis the day after her first injection, which did not allow her to return for her second injection. The last excluded participant was admitted to the emergency department for 12 hours for throat tightening and difficulty breathing that started 36 hours after her first injection. As requested by the treating physicians, the code was broken for the 2 latter patients, and both had received placebo.

Of the 146 participants in the analysis, 46 were in group A, 50 were in group B, and 50 were in group C (Table 1). In group B, 12 patients (24%) had a recurrence of ORS on revaccination in 2001-2002. In group C, 28 patients (56%) were affected by ORS in 2001 after receiving Fluvalir S/F and 20 (40%) were affected after receiving Vaxigrip. Significantly more group A participants were recruited in Vancouver (P < .001), and more group C participants were recruited in Quebec City. Older patients (≥60 years) were significantly less represented in group C than in the 2 other groups (4% vs 24% and 30%; P < .001). Men represented 23% of participants, and there were fewer in group C than in group A or B. The severity of the previous ORS episode seems to have been greater in participants with ORS in 2000 who were not revaccinated in 2001 (group A) than in those who were revaccinated (group B) and in patients with ORS in 2001 (group C). More participants in group A than in group B were prevented from conducting daily activities after their 2000 episode of ORS (41% vs 22%; P = .04), had a severity score between 7 and 10 (34% vs 13%; P = .02), and consulted a physician (39% vs 24%; P = .18).

All ORS-defining symptoms during the first 24 hours after injection were more frequent after vaccine than after placebo (Table 2). There was no difference in ORS symptoms between placebo and vaccine recipients between days 2 and 7. The frequency of ORS-defining symptoms after placebo was similar in all vaccine groups, but that after vaccine was approximately twice as frequent after Fluviral S/F use than after Vaxigrip use. In addition to bilateral red eyes, there was significantly more ocular pain or pruritus after vaccine than after placebo. All respiratory symptoms were more frequent after vaccine than placebo, but this was statistically significant only for sore throat, difficulty swallowing, cough, and chest tightness. Eyelid, lip, and facial edema were not signifi-

Table 1. Characteristics of the 146 Participants by ORS Group*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n = 46)</th>
<th>Group B (n = 50)</th>
<th>Group C (n = 50)</th>
<th>Total (N = 146)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quebec City, Quebec</td>
<td>17</td>
<td>34</td>
<td>68</td>
<td>40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Montérégie, Quebec</td>
<td>33</td>
<td>38</td>
<td>20</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Vancouver, British Columbia</td>
<td>50</td>
<td>28</td>
<td>12</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>18-39</td>
<td>22</td>
<td>20</td>
<td>34</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>35</td>
<td>20</td>
<td>38</td>
<td>31</td>
<td>.01</td>
</tr>
<tr>
<td>50-59</td>
<td>20</td>
<td>30</td>
<td>24</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>24</td>
<td>30</td>
<td>4</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>28</td>
<td>14</td>
<td>23</td>
<td>.20</td>
</tr>
<tr>
<td>F</td>
<td>74</td>
<td>72</td>
<td>86</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Severity of previous ORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Categorical score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present, not bothersome</td>
<td>13</td>
<td>40</td>
<td>50</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Interfered with daily activities</td>
<td>46</td>
<td>38</td>
<td>33</td>
<td>39</td>
<td>.002</td>
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<tr>
<td>Prevented daily activities</td>
<td>41</td>
<td>22</td>
<td>17</td>
<td>26</td>
<td></td>
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<tr>
<td>Numeric score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>20</td>
<td>40</td>
<td>50</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>41</td>
<td>40</td>
<td>26</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>7-10</td>
<td>33</td>
<td>12</td>
<td>12</td>
<td>18</td>
<td>.01</td>
</tr>
<tr>
<td>Not available</td>
<td>7</td>
<td>8</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Consulted a physician</td>
<td>39</td>
<td>24</td>
<td>13</td>
<td>25</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviation: ORS, oculorespiratory syndrome.

*Data are given as percentages unless otherwise specified. Group A includes patients who had ORS in 2000 but were not revaccinated in 2001; group B, patients who had ORS in 2000 and were revaccinated in 2001; and group C, patients who had ORS in 2001 but not in 2000.
Significantly more frequent after vaccine than after placebo (6% vs 3%; \(P = .17\)). Local injection site symptoms were reported in 50% of patients after vaccine compared with 3% after placebo (\(P < .001\)). Systemic symptoms in general were not significantly more frequent after vaccine than after placebo (19% vs 16%; \(P = .54\)).

There were 52 and 16 participants (36% and 11%) who had at least 1 ORS symptom in the 24 hours after vaccine and placebo, respectively. Six participants had 1 or more ORS symptoms after placebo and vaccine, and only 1 had 2 or more ORS symptoms. The risk of ORS recurrence was highly significant after receiving Fluviral S/F and at the limit of significance after receiving Vaxigrip (Table 3). The risk difference was approximately 2 times higher after receiving Fluviral S/F than after receiving Vaxigrip. When the case definition was more stringent and required 2 or more ORS symptoms, the risk difference remained significant (Table 3). When further tightening the case definition and requiring 1 symptom in the edema or ocular category and 1 respiratory symptom, only Fluviral S/F remained statistically significantly associated with ORS. The risk of ORS was 2 times higher in group A vs groups B and C (41% vs 16% and 18%). Stratification by vaccine and ORS group showed that only group A patients vaccinated with Fluviral S/F had a strong and consistent association with ORS with all case definitions. For the other subgroups, the risk of ORS was present but smaller, declined more rapidly with stringent case definitions, and was generally not statistically significant. In group B, of the 36 patients (72%) who reported no recurrence in 2001, 8 (22%) had a recurrence during this trial; of the 14 patients (28%) who reported a recurrence in 2001, 5 (36%) had a recurrence during the trial. In group C patients, the risk difference was similar regardless of the vaccine that triggered the ORS in 2001.

The symptoms experienced by patients after receiving Fluviral S/F or Vaxigrip were generally similar (Table 4). However, there was a greater proportion of patients with cough and chest tightness after receiving Fluviral S/F vs Vaxigrip. The severity of the symptoms was rated as not bothersome by 88% (27 patients) and 86% (18), respectively; interfered with daily activities in 13% (4) and 10% (2); and prevented daily activities in 0% and 5% (1). Although the frequency of ORS symptoms varied by group or vaccine, the severity was similar in each of the 3 groups and was not correlated with the severity of the previous episode.

### Table 2. Oculorespiratory Syndrome Symptoms in the First 24 Hours After Injection in All 146 Patients by Vaccine Group

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Fluviral S/F, * No. (%) (n = 73)</th>
<th>Vaxigrip, † No. (%) (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral red eyes</td>
<td>13 (18)</td>
<td>0‡</td>
</tr>
<tr>
<td>Ocular pain/pruritus</td>
<td>15 (21)</td>
<td>4 (5)§</td>
</tr>
<tr>
<td>Any</td>
<td>25 (34)</td>
<td>4 (5)‡</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>13 (18)</td>
<td>3 (4)§</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>7 (10)</td>
<td>0§</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (22)</td>
<td>2 (3)‡</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>6 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>5 (7)</td>
<td>2 (3)‡</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>12 (16)</td>
<td>0‡</td>
</tr>
<tr>
<td>Wheeze</td>
<td>3 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>28 (38)</td>
<td>6 (8)‡</td>
</tr>
<tr>
<td>Facial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid swelling</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Lip swelling</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Facial swelling</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>5 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site symptoms</td>
<td>32 (44)</td>
<td>0‡</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Chills</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (12)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Muscle ache</td>
<td>1 (1)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Joint ache</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>18 (25)</td>
<td>14 (19)</td>
</tr>
</tbody>
</table>

*Shire Biologics, Laval, Québec.
†Aventis Pasteur, Toronto, Ontario.
‡\(P < .001\).
§\(P < .05\).
days after their injection to guess whether they had received placebo or vaccine, 48% of vaccinated individuals believed that they had received placebo compared with 77% receiving placebo. There was no difference between vaccines.

The revaccination of individuals who have had a clinically significant adverse event is always concerning. After an ORS recurrence rate of 33% forced the early termination of a similar clinical trial the previous year,9 patients who experienced moderate-to-severe ORS in 2000 were advised to defer influenza vaccination in 2001-2002 if they were not at high risk of influenza complications or to consult experts if they were.3 Subsequent epidemiologic studies7,10 of the outcome of revaccination during that season were more reassuring. The present clinical trial demonstrates that patients who sustained ORS in 2000 and were not revaccinated (group A) had a high risk of recurrence when given the 2002-2003 Fluviral S/F. For Vaxigrip and for other subgroups, there seems to be a weak association, but our data are not conclusive. The other important conclusion from this study is that recurrences were mild: 86% of patients rated its severity as mild (bothersome but did not interfere with their daily activities), and nearly all patients (94%) said that they would agree to be revaccinated the
following year. This is similar to previous surveys that showed that most recurrences were mild, with patients wanting to receive influenza vaccine in the future.

The absence of a laboratory test to confirm ORS and the need to rely only on a clinical case definition remains an important limitation of any study of ORS because patients affected by ocular or upper respiratory tract infections would qualify as ORS cases. The National Advisory Committee on Immunization 2001 ORS case definition is nonspecific and somewhat subjective. The crossover design minimizes the variance of the subjective part because the same patients assess the placebo and the vaccine. To compensate for the lack of specificity of the primary analysis, we performed secondary analyses using more stringent and more specific case definitions that are more clinically significant. It is reassuring that results of that study, in which most participants were from Quebec City, were similar to those in group A in the present trial, it seems reasonable to attribute the results to the group and not to the site.

The European incident in 1995-1996, the cases reported in the United States, and the Canadian experience in 2000, 2001, and 2002 all suggest that ORS can occur with multiple influenza vaccines at a frequency that varies by product or season. This frequency is likely to be no more than very low in regular years, as evidenced by a variety of clinical trials conducted with the influenza vaccines during different years and in different locations. It is possible that patients vaccinated with influenza vaccine who sustain ORS have previously been misdiagnosed as being allergic to influenza vaccine. The harm in this misclassification should be recognized because many individuals may be advised not to be revaccinated, thus denying them the benefit of protection from a potentially deadly infection. It is reassuring that in no patient in this trial had anaphylaxis on revaccination. Including this study, more than 500 persons previously affected by ORS have been revaccinated and followed up in different studies, and no anaphylaxis has been reported. The pathogenesis of ORS is currently unknown, but skin testing has confirmed that ORS is not an IgE-mediated (anaphylactic) type of hypersensitivity. This study shows that revaccination of patients with ORS is safe and that distinguishing ORS from an allergic reaction is a worthwhile undertaking. A biological marker for ORS remains elusive, but skin testing by an allergist can rule out anaphylaxis and should be performed before recommending that a patient should never again be vaccinated.

In conclusion, vaccine providers should reassure patients with ORS that this experience is not a contraindication to revaccination. Although recurrence is possible, such episodes are likely to be mild and should be balanced against one’s own personal risk of influenza infection and the complications that follow in failing to be immunized.

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Correspondence: Gaston De Serres, MD, PhD, Institut National de Santé Publique du Québec, 2400 d’Estimauville, Québec, Québec, Canada G1E 7G9 (gaston.deserres@ssss.gouv.qc.ca).
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Table 4. Distribution of ORS Symptoms (Only After Injection of Vaccine) by Vaccine Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluviral S/F Group</td>
</tr>
<tr>
<td>≥1 ORS symptom</td>
<td>n = 31</td>
</tr>
<tr>
<td>Ocular (any)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Bilateral red eyes</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Ocular pain/pruritus</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Respiratory (any)</td>
<td>28 (90)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (52)‡</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>12 (39)‡</td>
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<td>Wheeze</td>
<td>3 (10)</td>
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<tr>
<td>Edema (any)</td>
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<td>Eyelid swelling</td>
<td>4 (13)</td>
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<tr>
<td>Lip swelling</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Facial swelling</td>
<td>2 (6)</td>
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<td>More stringent case definitions</td>
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<tr>
<td>≥2 ORS symptoms</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Ocular symptoms or edema</td>
<td>15 (48)</td>
</tr>
<tr>
<td>plus respiratory symptoms</td>
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Abbreviation: ORS, oculo-respiratory syndrome.
*Shire Biologics, Laval, Québec.
†Aventis Pasteur, Toronto, Ontario.
‡P < .05.


Omission of Financial Disclosure. In the Original Investigation by De Serres et al titled “Recurrence Risk of Oculorespiratory Syndrome After Influenza Vaccination: Randomized Controlled Trial of Previously Affected Persons,” published in the November 8 issue of the ARCHIVES (2004;16;2266-2272), the Financial Disclosure was inadvertently omitted on page 2266. The statement of Financial Disclosure should have appeared beneath the Author Affiliations and read as follows: “Financial Disclosure: Drs De Serres, Skowronski, and Duval have received research grants and Dr Skowronski has received honoraria from Aventis Pasteur and Shire Biologics. Dr Guay has received grants from Wyeth-Ayerst Canada, Biochem Pharma, and Merck Frosst Canada.” The journal regrets the error.