Adverse events following live-attenuated intranasal influenza vaccination of children with cystic fibrosis: Results from two influenza seasons

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Abstract

Background: Despite the approved use of live-attenuated intranasal influenza vaccine (LAIV) for seasonal immunization of patients with cystic fibrosis (CF), many questions remain unanswered regarding the timing, duration, and types of adverse events that occur following administration of this vaccine.

Methods: In 2012 and 2013, 264 LAIV doses were administered to 198 patients aged 2–19 with CF. Vaccinees were followed prospectively for 55 days after vaccination (day 0) and information on adverse events was collected. Bayesian change-point analysis was used to identify the risk period following LAIV during which participants had a higher risk of reporting adverse events. Multivariable zero-inflated Poisson regression models were then used to estimate the adjusted incidence rate ratio (aIRR) and 95% credible interval (CrI) of reporting each adverse event in the risk period versus the control period.

Results: There was a higher risk of reporting serious adverse events (SAEs) (aIRR 1.45, 95% CrI (0.29, 5.17)) and solicited symptoms during days 0–6 of follow-up compared to control period days 7–55. However, most SAEs were not causally related to LAIV and the solicited symptom episodes were brief, usually lasting 1–2 days. There was no increased risk of antibiotic prescriptions for respiratory conditions in the risk vs. control periods (aIRR 0.48, 95% CrI (0.23, 0.91)).

Conclusions: Adverse events were most common 0–6 days after LAIV administration but were generally benign and self-limiting. Pulmonary exacerbations did not increase in frequency.

1. Introduction

Cystic fibrosis (CF) is characterized by chronic pulmonary disease that is periodically interrupted by acute deteriorations in clinical status called pulmonary exacerbations (PEs) [1]. While there is no consensus on the exact definition of PEs [2–5], the most common clinical symptoms include coughing, wheezing, increased sputum production and decreased pulmonary function. PEs require medical care (often hospitalization) and are associated with decreased health-related quality of life [6] and increased mortality [7].

Viral-related PEs are associated with worse severity and quality of life scores compared to non-viral exacerbations [8]. Influenza viruses, in particular, have been shown to be involved in PEs [8–10]. Seasonal influenza vaccination is thus recommended for patients with CF, although current evidence supporting routine influenza vaccination in this population is limited [11]. In Canada,
both the live-attenuated intranasal influenza vaccine (LAIV) and the injectable intramuscular vaccine are recommended for children and adolescents with CF. LAIV was incorporated in publicly funded Canadian vaccination programs in 2012 and is preferred by caregivers and patients over the trivalent inactive vaccine (IIV3) administered by intramuscular injection [12]. In the U.S., the American Advisory Committee on Immunization Practices voted that LAIV not be used in the 2016–2017 influenza season. The most frequently cited hypotheses for the poor relative performance of LAIV compared to IIV3 include inadequate replicative fitness of the a(H1N1)pdm09 LAIV strains, vaccine-virus interference in the quadrivalent formulation of the vaccine, reduced replication of LAIV-strain viruses due to pre-existing anti-influenza virus immunity from previous influenza vaccinations and poor thermostability of the a(H1N1)pdm09 LAIV strains [13]. However, as previously stated, LAIV continues to be used in several countries including Canada. LAIV continues to be recommended for use in children in the U.K. [14], Finland [15] and Canada, as studies conducted in these countries demonstrate an overall protective effect of LAIV in children and adolescents.

Despite the acknowledged importance of seasonal vaccination against influenza viruses for patients with CF, limited novel research exists evaluating the safety of LAIV in this population [16–18]. This leaves many questions unanswered regarding the frequency, timing, duration, type and severity of adverse events that occur following LAIV. Our primary objectives were thus to estimate the exact period following LAIV during which pediatric vaccinees with CF were at the highest risk of adverse events (AEs) and to estimate the relative incidence of AEs following LAIV in this risk period compared to a control period. A secondary objective was to explore whether subsequent revaccination with LAIV affected the risk of AEs [19]. Results may be used to accurately characterize the risk period following LAIV in order to optimize recommendations and AE surveillance following LAIV.

2. Methods

2.1. Study design and population

A prospective self-controlled risk interval study design was used to compare the incidence of AEs during a risk and control period in the 55 days following LAIV [20,21]. The study population consisted of individuals with CF between 2 and 19 years of age recruited from 4 specialized CF clinics in Canada at which they were registered for regular CF care either that were vaccinated for the first time. Although LAIV was available previously on the market, 2012–13 was the first year when LAIV was publicly funded for children with underlying medical conditions (including CF), 2–17 years of age, in Québec [27]. Similarly, participants recruited from British Columbia in the second study year were receiving LAIV for the first time.

2.2. Data collection

After obtaining informed consent/assent from participants and/or their parents, data were collected prospectively for 55 days after day 0 (vaccination day). Participants recorded any antibiotic prescriptions and all-cause hospitalizations (whether at a participating hospital or not) that occurred throughout follow-up. Participants also filled out a daily diary checklist for respiratory, gastrointestinal, localized and systemic symptoms. Trained research nurses collected these data by phone on study days 1, 7, 14, 21, 28, 42 and 55. The methodology used to ascertain all outcomes was consistent between both study years.

2.3. Vaccination

Until 2014, LAIV was trivalent. In both 2012–13 and 2013–14 LAIV contained an A/California/7/2009 (H1N1) pdm09-like virus and an A/Victoria/361/2011 (H3N2)-like virus. In the 2013–14 season, the type B strain changed from a B/Wisconsin/1/2010-like strain (Yamagata-line) to a B/Massachusetts/2/2012-like virus [26]. Recruited participants did not receive LAIV concurrently with other vaccines nor did they receive any other vaccines throughout the 2 months of follow-up (including another dose of LAIV). In the first study year (2012–13), none of the participants had previously received LAIV. Although LAIV was available previously on the market, 2012–13 was the first year when LAIV was publicly funded for children with underlying medical conditions (including CF), 2–17 years of age, in Québec [27]. Similarly, participants recruited from British Columbia in the second study year were receiving LAIV for the first time.

2.4. Ethics

The research ethics boards of the four participating hospital sites approved the initial data collection for this study. This data analysis was approved by the McGill University Health Center Research Ethics board. All participants (or their parents) provided informed consent/assent prior to enrolment.

2.5. Outcomes of interest

The evaluated outcomes were categorized into three types of AEs: a strictly defined outcome, a conservatively defined outcome and a very broad class of outcomes that may be related to the other two outcomes on a theoretical scale of increasing morbidity (Appendix Table 1).

First, we considered serious adverse events (SAEs) as defined by the International Conference on Harmonization’s Consolidated Guidance for Good Clinical Practice (ICH-E6) [28]. SAEs were the most strictly defined AE. Principal investigators in each study site assessed the possible causal relationship between LAIV and SAEs using the International Conference on Harmonization E2A Guideline [29] and the World Health Organization (WHO)-Uppsala Monitoring Center system for standardized case causality assessment [30]. SAEs were classified as PEs during the analysis stage by a pediatric respirologist (LL).

Second, antibiotic prescriptions for respiratory problems were considered as proxies for PEs that may not have been captured by the SAE definition [31].

Third, all symptoms recorded in patient diaries (henceforth referred to as solicited symptoms) were the broadest set of outcomes evaluated. These symptoms are part of the Public Health Agency of Canada’s standard assessment of post-vaccination AEs [32]. We considered symptom episodes to be independent if their reported onset was separated by ≥2 days.

2.6. Statistical analyses

2.6.1. Risk period following vaccination

We hypothesized that the risk of AEs was not homogeneous throughout a previously considered [25,33] 4-week risk period following LAIV. We thus conducted a Bayesian change-point analysis (BCPA) to identify a single change point in the outcome (the daily count of participants reporting at least one solicited symptom). BCPA is used to simultaneously estimate the location of a change-point, and the rates at which events occur before and after
the change-point, with corresponding 95% credible intervals (CrIs) (Appendix Section III (3.01)). Gibbs sampling was used to draw samples from the posterior distributions across all unknown parameters [34].

2.6.2. Regression models: All outcomes

Using the optimal cut-off point in time from the BCPA, the adjusted incidence rate ratio (aIRR) of reporting an AE in the risk period versus the control period was initially estimated using multivariable Poisson regression models [35]. A regression model was run for each outcome. Given the large number of zero counts observed for SAEs and antibiotic prescriptions, aIRRs were also estimated using Zero-inflated Poisson (ZIP) regression models. ZIP results are also presented for solicited symptoms since the probability of excess-Poisson zero counts was estimated to be non-zero for all of these outcomes.

An offset term (log(person-days)) was included in all regression models. Since information on the exact period of hospitalization was not available, we considered 14 days for each hospitalization as time during which a participant could not experience another SAE [36]. No person-time was removed from the denominators of the aIRRs for antibiotic prescriptions, as participants were theoretically at risk of having another antibiotic prescribed even if already on antibiotics. Exact person-time was removed for the duration of all solicited symptoms.

Correlation arising from the representation of each participant twice (once in the risk and once in the control periods) was accounted for by allowing the intercept of each regression model to vary by subject. This hierarchical structure also accounted for any extra-Poisson variability owing to mixing individual with different rates. Furthermore, all models were adjusted for the confounding effects of the seasonal circulation of non-influenza respiratory viruses and study year (Appendix Section III (3.02)). Confounders were chosen based on biological plausibility and in consultation with subject matter experts.

All analyses were stratified by receipt of LAIV in the previous influenza season. Non-informative prior distributions were used for all analyses. The median, 2.5% and 97.5% of the estimated posterior distributions were used as the aIRR point estimate, lower and upper limits of the 95% CrIs, respectively. Markov Chain Monte Carlo convergence was assessed by visual inspection of history, trace and quantile plots. Inferences were calculated via the Gibbs sampler algorithm as implemented in WinBUGS (Version 1.4.3, MRC Biostatistics Unit, Cambridge, UK). Descriptive statistics and graphics were generated using Stata 13® and Microsoft Excel.

2.6.3. Sensitivity analyses

We evaluated the robustness of our results by modifying three key definitions/assumptions and re-analyzing our data. First, we checked the robustness of the results obtained in the BCPA by estimating the IRR of each outcome (using ZIP regression) using two alternative risk periods: days 0–14 (control period: days 15–55) and days 0–21 (control period: days 22–55). Second, the decision to consider a solicited symptom episode as incident if the preceding 48 h were event-free may have incorrectly estimated the number of symptom episodes. We thus compared the number of incident reported solicited symptom spells using 3, 5 and 7 event-free days prior to spell initiation (i.e. the first day an episode, or spell, of AE was reported) to define an independent symptom episode. Third, we re-calculated all IRRs for the risk period obtained in the BCPA using the same ZIP regression models but adjusting for the seasonal circulation of other respiratory viruses including influenza.

3. Results

No outcome, exposure or confounder data was missing. Overall, 198 participants were recruited over the 2 study years, representing roughly 12% of the Canadian population with CF between the ages of 2–19 [37] and 264 vaccine doses were monitored throughout the 2 study years (Fig. 1). The mean age of study participants at the time of vaccination was 10.6 years (standard deviation 4.77) and 51% (135/264) were female. Eighty-one percent of participants were vaccinated against influenza in the previous season (213/262), with 66 re-recruited participants from Quebec study sites receiving LAIV for 2 consecutive influenza seasons. There were no losses to follow-up. This is not surprising given the short follow-up period, the multiple contact points throughout follow-up between participants and research nurses and the fact that participants and their parents have multiple contacts with healthcare providers throughout the year for regular CF-related care.

3.1. Risk period

For the entire study cohort, the risk of reporting at least one solicited symptom was highest in days 0–6 following vaccination (Table 1). This risk period was similar (days 0–5) for subjects that had received LAIV for two consecutive influenza seasons and for those receiving LAIV for the first time (Fig. 2, Table 1). Follow-up days 0–6 were thus considered the risk period and days 7–55 as the control period in the main analyses. For results from all regression models (both Poisson and ZIP) and for all outcomes see Appendix Section IV.

3.2. Serious adverse event incidence rate ratios

In total, 15 SAEs were reported by 15 different study participants, all of whom were hospitalized (no deaths; see Appendix Sec-

<table>
<thead>
<tr>
<th>Study site</th>
<th>Study year</th>
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<tbody>
<tr>
<td>CHUQ-CHUL Quebec</td>
<td>2012-13</td>
</tr>
<tr>
<td>55 participants</td>
<td></td>
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<tr>
<td>37 participants</td>
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<tr>
<td>MCH Quebec</td>
<td>2013-14</td>
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<tr>
<td>47 participants</td>
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<tr>
<td>29 participants</td>
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<tr>
<td>STJ Quebec</td>
<td>2012-13</td>
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<tr>
<td>66 participants</td>
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<td>-</td>
<td>2013-14</td>
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<tr>
<td>BC Children’s British Columbia</td>
<td>2013-14</td>
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<tr>
<td>30 participants</td>
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Fig. 1. Number of study participants by study year and study site; arrows correspond to first year cohort participants that were re-recruited in the second study year.
tion II Table 1). The four SAEs in study year 2 were observed in participants receiving LAIV for a second consecutive influenza season. Furthermore, 2/15 SAEs (days 16 and 30) were determined by investigators to “possibly” be causally related to LAIV and 9/15 SAEs were determined to be PEs \textit{a posteriori} (one participant each on days 3, 23, 26, 41, 42, 50, 52 and two participants on day 16). Of note, the SAE that occurred on day 30 of follow-up was a hospitalization for an intestinal sub-occlusion. In total, three SAEs occurred in the risk period (1833 person-days) and 12 in the control period (12,789 person-days), corresponding to a ZIP model-estimated aIRR 1.45, 95% CrI (0.29, 5.17) (Fig. 4, Appendix Section IV Fig. 3). The numerical values of the point estimates and 95% CrIs in Fig. 4 are found in Appendix Section IV Table 2. In first-time LAIV recipients the ZIP-estimated aIRR = 2.23 (95% CrI: 0.44, 9.04) and in those receiving LAIV for a second consecutive influenza season aIRR = 0.001 (95% CrI: 2.17E-10, 1.78).

A total of 164 antibiotic prescriptions were reported during the two study years, 92% (151/164) of which were prescribed for respiratory problems. Amoxicillin-clavulanic acid, sulfamethoxazole-trimethoprim and cephalexin accounted for almost half of all prescriptions for respiratory-related conditions (Appendix Fig. 1). The numerical values of the point estimates and 95% CrIs in Fig. 4 are found in Appendix Section IV Table 2. In first-time LAIV recipients the ZIP-estimated aIRR = 2.23 (95% CrI: 0.44, 9.04) and in those receiving LAIV for a second consecutive influenza season aIRR = 0.001 (95% CrI: 2.17E-10, 1.78).

Overall, participants had an increased risk of all reported solicited symptoms in days 0–6 following vaccination compared to days 7–55 following vaccination. Chest congestion, increased sputum and wheezing were the three respiratory conditions for which participants had the largest increased risk (Table 2; Fig. 4; see Appendix Fig. 4). There were more fever episodes reported than any other symptom during days 0–6 of follow-up regardless of previous vaccination status (Table 2). Subjects receiving LAIV for the first time reported longer and more frequent episodes of solicited symptom during days 0–6 of follow-up compared to those receiving LAIV for the second consecutive influenza season (Fig. 3).

3.3. Sensitivity analyses

The aIRRs of reporting most AEs decreased when the risk period was altered to days 0–14 and 0–21 of follow-up (compared to the original day 0–6 risk-period), with the exception of four solicited symptoms (arthralgia, coughing, dyspnea and vomiting) (Fig. 4; Appendix Table 1). Considering days 0–6 of follow-up as the risk period for most AEs following LAIV is thus an acceptable definition. Furthermore, we found that using a cutoff time of 2 days event-free prior to spell initiation appears to be a stable definition and would at most over-estimate the number of reported episodes of AEs (Appendix Section V). Finally, similar to the results obtained when
influenza was excluded from the background rate of respiratory virus circulation, the aIRR point estimates calculated with influenza included in the seasonality variable were either \(1/2\) or \(1/4\) for all AEs during the risk period compared to the control period (Appendix Section IV). However, the point estimates and CrIs did change for many symptoms. This is not surprising given the imperfect effectiveness of LAIV observed in healthy children [38] coupled with the fact that the natural circulation of influenza viruses was observed to be variable between the risk and control periods for many participants (Appendix Fig. 2A–C).

4. Discussion

Overall, we found that the risk of reporting any solicited symptoms in the two months following LAIV was highest during the week following vaccination (days 0–6). Since LAIV contains live viruses, antigen exposure begins immediately at inoculation and the pathogenesis of tissue damage or clinical disease arises due to immune-mediated reactions to vaccination with live viruses and/or viral replication and activity (i.e. cytolytic infection). The marginally shorter risk period observed in re-vaccinees may relate to a primed immune response to LAIV antigens since 2/3 influenza virus strains contained in LAIV in 2012–13 were the same as those in 2013–14 [39].

Few hospitalizations were observed throughout the 2-month study period and almost all were deemed not causally related to vaccination by study investigators. Since the criteria used to assess causality include temporality and propensity for an alternative explanation (such as concurrent health problems), it is likely that the latter criterion was used in this case although further
information was not available. Our aIRR results (for day 0–6 risk period vs. day 7–55 control period) are similar to those published in a recent self-controlled case-series study evaluating all-cause hospitalizations in children 2–18 years old with non-asthma, non-immunocompromising underlying conditions [40].

We observed no increased risk of antibiotic prescription in the week after vaccination compared to the subsequent 7 weeks, and the risk of antibiotic prescription for respiratory problems remained small regardless of the length of risk period used (Fig. 4). Of note, the aIRR corresponding to a risk-period of days 0–21 was the largest of the three risk periods compared, perhaps due to the delayed onset of secondary bacterial infections. While we found an increased risk of reporting all solicited symptoms in the first week compared to subsequent weeks following LAIV, these symptom episodes were brief, often lasting 1–2 days. Similar to results reported in a Cochrane review [41], the most common AEs reported during the entire two-month follow-up were fever, tiredness, headache, cough and rhinorrhea. Furthermore, eye redness was reported more often in the first study year than in the second study year. However, the incidence of oculo-respiratory syndrome (ORS) [42] in the entire cohort could not be evaluated since facial swelling and pharyngitis (two symptoms that may be part of the ORS constellation) were not solicited in both study years [25].

Results of this study must be interpreted with regard to several limitations. First, the misclassification of subjective symptoms and measurements ascertained from participants’ non-validated daily diaries is possible [43]. However, the risk of bias caused by this misclassification was minimized in this study given the multiple contact points between research nurses and participants in both the risk and control periods. Second, we observed a signal for decreasing risk of all outcomes in vaccinees receiving LAIV for two consecutive influenza seasons. However, our small sample size of re-vaccinees precludes any definitive conclusions. Also, the shifting of the aIRR in re-vaccinees towards the null may indicate a selection bias arising from the depletion of individuals.
susceptible to the adverse effects of LAIV in the second study year [44]. Of note, time-varying confounding is unlikely in this study given that changes in important time-varying confounders (such as CF disease progression and age) are negligible in a 2-month time span [45] and most medications were ongoing throughout the study period. It should also be noted that another limitation of the study is the fact that the exact criteria used to ascribe causality were not available, making it problematic to extend conclusions of this assessment as it is unclear to what extent it is prone to bias. However, the methodology used corresponds to the standard as proposed by the WHO.

Results from this study support the safety of LAIV in patients with CF between the ages of 2–19 years. Further research with a sufficient sample size should evaluate the potential change in risk of AEs in LAIV re-vaccinees. Our study findings are generalizable to all children and adolescents in Canada with CF that are indicated for LAIV and are also likely generalizable to the analogous population in other developed countries in the Northern Hemisphere (with the caveat of potential differences in distribution of CF genotypes in these regions). These results are also likely applicable to quadrivalent LAIV [46,47].

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Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.07.068.

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