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Risk factors associated with anaphylaxis and other allergic-like events following receipt of 2009 monovalent AS03-adjuvanted pandemic influenza vaccine in Quebec, Canada

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ABSTRACT

Introduction: In Quebec, Canada, receipt of the 2009 AS03-adjuvanted pandemic H1N1 vaccine was associated with increased risk of anaphylaxis and other allergic-like events (ALE), especially among women of childbearing age. In response to this safety signal, a case–control study was conducted to identify potential risk factors.
Methods: A total of 435 ALE (50 anaphylaxis) occurring <24 h following pandemic vaccination were compared to 849 age-gender matched controls randomly selected from the provincial Pandemic Influenza Vaccination Registry. More than 60 potential risk factors were evaluated through phone interviews and included demographic information, medical history, medication use or acute respiratory illnesses (ARI) concurrent with vaccination and other risk factors associated with general allergy. Odds ratios (ORs) with 95% confidence intervals were estimated with unconditional logistic regression.
Results: Factors associated with increased risk of anaphylaxis included concurrent ARI (18% cases vs. 4% controls, ORadj 7.67, 95%CI: 3.04–13.37), food allergy (26% cases vs. 4% controls, ORadj 3.84, 95%CI: 1.51–9.74) and vaccination during the first four weeks of the campaign (66% cases vs. 50% controls, ORadj 2.16, 95%CI: 1.10–4.25) whereas alcohol exposure (≥1 drink/week) was associated with reduced risk (29% cases vs. 42% controls, ORadj 0.26, 95%CI: 0.13–0.57). These factors were also significantly associated with any ALE but the strength of association was weaker. Allergy to components found in the vaccine (e.g., egg, thimerosal) was infrequent and did not significantly differ between cases and controls.
Conclusion: Increased anaphylaxis and other allergic-like events observed in association with AS03-adjuvanted pandemic H1N1 vaccine remain mostly unexplained despite extensive risk factor review. However, prior to mass vaccination with similar formulations this safety signal warrants further consideration and better understanding. In particular, the predominance among women of childbearing age may be a clue to underlying biological or hormonal influences on adverse immunological responses to vaccine.

1. Introduction

In 2009 in Quebec, Canada, the population was vaccinated in public health clinics mostly with an AS03-adjuvanted monovalent pandemic influenza A(H1N1)pdm09 vaccine (Arepanrix®, GlaxoSmithKline) By the end of the campaign, ~4.4 million doses of AS03-adjuvanted vaccine had been administered and overall AEFI reporting rates for pandemic vaccines were 2–3 times greater than usually seen with non-adjuvanted seasonal trivalent inactivated vaccines (TIV) (51 vs. 19 cases per 100,000 doses) [1]. While general reporting was probably stimulated by the mass campaign and the use of a new adjuvanted product, there was a disproportionate reporting of allergic-like events (ALE). The rate of anaphylaxis alone reached 8 cases per million doses a 20-fold increase compared to

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the rate of 0.4 per million TIV doses reported during the previous 6 seasons [1]. This differential increase in reporting suggested that anaphylaxis and other allergic-like events could not be explained by stimulated reporting alone. Since 2010–2011, the reporting rates for anaphylaxis and other allergic-like events observed with seasonal vaccine have returned to baseline levels (0.1–0.2 and 1.7–2.7 per 100,000 doses, respectively), although seasonal trivalent vaccines used since 2010 contain no adjuvant but the same pandemic influenza strain and a greater amount of hemagluttinin (15 vs. 3.75 μg).

Approximately 75% of ALE reports came from women (60% of which were of childbearing age) and dose-adjusted rates of anaphylaxis were four times higher in women than in men (11.5 vs. 3.0 per million doses, respectively). Reports also came disproportionately from healthcare workers, who were twice as likely than other vaccinees to report an allergic-like event following pandemic vaccination. While 41% of cases reported a history of allergy to either food, drugs or respiratory allergens, clinical investigations conducted among nearly 100 reported cases showed that few, if any, were IgE-mediated [2,3].

Research related to post-vaccination ALE has generally focused on vaccine constituents that may be associated with anaphylaxis (e.g., gelatin, egg proteins, latex, antibiotics) whereas host and environmental factors have rarely been studied [4,5]. Immunological mechanisms involved in anaphylaxis may be IgE-dependent (e.g., foods, venoms, medications, latex) or independent (e.g., radiocontrast media (RCM), NSAIDs, Dextran) [6–8]. Direct, non-immunologic, mast cell activation has also been demonstrated with alcohol, opiates, and RCM. Risk of anaphylaxis is affected by age, gender, concomitant diseases (e.g., pulmonary and cardiovascular disease, atopy), concurrent medication, or alcohol use [4–8]. Several other factors can amplify the severity of anaphylactic episodes (e.g., physical activity, acute infection, premenstrual status, ß-adrenergic blockers, and angiotensin-converting enzyme (ACE) inhibitors) and can interact synergistically [9]. Whether these risk factors influence the risk of postvaccination ALE is unknown.

The high reporting rate of anaphylaxis and other ALE following A(H1N1)pdm09 vaccination in Quebec led to concern for subsequent seasonal TIV containing the same pandemic viral antigen. An epidemiological investigation was mandated to better understand and quantify factors possibly contributing to vaccine-associated ALE. This matched case–control study assessed medical conditions, medications or other factors potentially associated with anaphylaxis and other ALE following monovalent AS03-adjuvanted influenza A(H1N1)pdm09 vaccine receipt.

2. Methods

2.1. Setting and study design

This age–sex frequency matched case–control study was conducted between May 20 and July 20, 2010, approximately 5–8 months after the pandemic vaccination campaign. The investigation was implemented through provisions of the Public Health Act and without requirement for ethics review [10].

We identified allergic-like events following pandemic H1N1 vaccination reported to the Quebec Adverse Event Surveillance System database (known as ESPRI) under diagnoses of “anaphylaxis”, oculorespiratory syndrome (ORS) or “allergy” (e.g., bronchospasm, oedema of the mouth/throat, facial/generalized oedema, urticaria or pruritic rashes). Details pertaining to the passive AEFI surveillance in Quebec have been previously described [2]. Deceased patients, those with symptom onset >24 h after vaccination, and the elderly aged ≥65 years (who were not prioritized for pandemic vaccination owing to impressions of lower risk and pre-existing antibody protection) were excluded.

For each case, two controls were randomly selected from the Pandemic Influenza Vaccination Registry (PIVR) established to record every dose of pandemic vaccine administered in the province along with relevant patient identifiers and demographics, and additional key vaccine-related characteristics (lot number, etc.) [1]. As the female-to-male ratio among cases was 1:1 before 14 years of age and 3:1 between 14 and 64 years, controls were frequency-matched by gender respecting the female-to-male ratio observed in the two age groups (<14 years or 14–64). We excluded controls who, upon recruitment, reported AS ≤24 h after vaccination or anaesthesia/paresthesia ≤72 h (due to another ongoing case–control study) [12]. Cases or controls unable to speak French or English were also excluded.

2.2. Data collection and study variables

Trained nurses conducted standardized phone questionnaires with all study participants or, for minors <14 years old, the child’s parents or legal guardians. Each sign and symptom required to apply the Brighton case definition of anaphylaxis and the ORS case definition of Canada’s National Advisory Committee on Immunization (NACI) were systematically queried. For cases and controls, we also collected demographics, personal and family medical conditions, obstetrical history (para, gravida, aborta), use of medication within 48 h of vaccination, the presence of an acute respiratory illness (ARI) at the time of vaccination (e.g., fever, respiratory infection, or influenza-like illness), reported allergy to potential allergenic components of the vaccine (i.e. eggs, fish, shellfish, thimerosal, latex), regular alcohol use and physical activity. Medications were classified according to first and second levels of the Anatomical Therapeutic Chemical (ATC) classification system [13]. Alcohol exposure and obstetrical history were not assessed in children <14 years old.

2.3. Case definitions

Because of the overlap in clinical criteria required to meet the BCCD of anaphylaxis and the NACI definition of ORS, clinical case definitions were applied sequentially. Cases were first classified for anaphylaxis then were assessed for ORS. Cases that did not meet either definitions were left categorized as ALE.

The Brighton Collaboration Case Definition (BCCD) was only applied to all reported ALE cases with symptom onset <1 h after vaccination [14], as anaphylaxis caused by an injectable antigen is expected to occur rapidly after administration. To classify remaining cases, we applied the NACI case definition of ORS defined as bilateral red eyes, and/or facial swelling, and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing/throat tightness, hoarseness or sore throat) with onset ≤24 h after influenza vaccination [11]. To improve specificity, patients who experienced pruritic rashes, a symptom typically absent with ORS, were not eligible as ORS cases [15]. All remaining allergic-like events (ALE) were sub-classified either as “immediate” (i-ALE) if symptom onset was <4 h, or as “delayed” (d-ALE) if symptom onset was ≥4 h after vaccination [16].

2.4. Statistical analyses

Separate unconditional regression models were built for BCCD-Anaphylaxis, NACI-ORS, i-ALE, d-ALE, and all allergic-like events. Respective odds ratios and 95%CI (OR [95%CI]) adjusted for sex and age group used for frequency-matching (<14 years/14–64 years) were estimated for potential risk factors. Variables associated with the outcome at a significance threshold of $p = 0.20$ were