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Safety and immunogenicity of 2010–2011 H1N12009-containing trivalent inactivated influenza vaccine in children 12–59 months of age previously given AS03-adjuvanted H1N12009 pandemic vaccine: A PHAC/CIHR Influenza Research Network (PCIRN) study

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ABSTRACT

Background: Concern arose in 2010 that reactogenicity, particularly febrile seizures, to influenza A/H1N1-containing 2010–2011 trivalent seasonal inactivated influenza vaccine (TIV) could occur in young children who had been previously immunized and/or infected with the pandemic strain. We conducted a pre-season study of 2010–2011 TIV safety and immunogenicity in children 12–59 months of age to inform public health decision making.

Methods: Children immunized with 1 or 2 doses of the pandemic vaccine, with or without the 2009–10 TIV, received 1 or 2 doses of 2010–11 TIV in an observational, multicentre Canadian study. Standard safety monitoring was enhanced by a telephone call at ~24 h post-TIV when adverse events were expected to peak. Summary safety reports were rapidly reported to public health before the launch of public programs. TIV immunogenicity was assessed day 0, and 21 days after final vaccination. Clinical Trials Registration NCT01180621.

Results: Among 207 children, a general adverse event was reported by 60.9% of children post-dose one and by 58.3% post-dose two. Only severe fever (>38.5 °C) was more common in two-dose compared to one dose recipients (16.7%, $n = 4$ v. 1.0%, $n = 2$). At baseline 99.0% of participants had A/H1N1 hemagglutinin inhibition (HAI) titers ≥10, and 85.5% had a protective titer of ≥40 (95% CI 80.0, 90.0). Baseline geometric mean titers (GMT) were higher in recipients of a 2-dose schedule of pandemic vaccine compared to one-dose recipients: 153.1 (95% CI 126.2, 185.7) v. 78.8 ((58.1, 106.8, $p < 0.001$). At 21 days, all regulatory criteria for influenza vaccine immunogenicity were exceeded for A/H1N1 and H3N2, but responses to the B antigen were poor. No correlations between reactogenicity and either baseline high influenza titers or serologic response to revaccination were evident.

Conclusions: Infants and toddlers who received AS03-adjuvanted A/H1N1 2009 vaccine up to 11 months earlier retained high titers in the subsequent season but re-exposure to A/H1N1 2009 antigen in TIV resulted in no unusual adverse effects and 100% were sero-protected for A/H1N1 after receipt of the 2010–11 TIV.

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1. Introduction

During the A/H1N12009 influenza pandemic, a universal immunization program with monovalent oil-in-water (squalene/tocopherol) adjuvanted vaccine was offered to Canadians. Attack rates of the A/H1N1 strain were high in young children, particularly those under five years of age, and thus they were priorized for pandemic vaccine. Given the robust immunogenicity of these adjuvanted vaccines [1–5] and high attack rates of A/H1N1 in young children [5], there was a concern that high levels of pre-existing immunity could be associated with increased reactogenicity upon exposure to pandemic strain antigens included in the 2010–2011 seasonal unadjuvanted TIV.

Public confidence in immunization programs is necessary to ensure vaccine coverage rates are sufficient to prevent influenza transmission to those at highest risk of influenza complications both by direct and indirect protection. A vaccine thought to be more reactogenic than 'normal' is less likely to have broad uptake, particularly if the disease prevented by the vaccine is not perceived as serious. Given the variable immunogenicity, effectiveness and reactogenicity of influenza vaccines given to infants and young children, and the possibility of increased reactions to 2010–2011 TIV [6], we sought to complete a pre-season safety trial to inform decision making prior to the initiation of public health programs, and to assess immune responses to TIV in children whose first exposure to antigens from a new influenza strain (vaccination ± infection) as well as a novel adjuvant occurred during the 2009 pandemic.

2. Materials and methods

This was a prospective, multicentre, unblinded observational study evaluating safety and immunogenicity of 2010–2011 TIV in young children who had received monovalent oil-in-water (squalene/tocopherol)(AS03) – adjuvanted influenza A H1N1 2009 vaccine *Arepanrix*™ (GlaxoSmithKline Biologicals, Laval, PQ) during 2009–2010.

2.1. Study population

Eligible children were 12–59 months of age, were generally healthy or had stable chronic conditions without immune compromise, and had received one or two doses of monovalent AS03-adjuvanted influenza A H1N1 2009 vaccine (*Arepanrix*™ GlaxoSmithKline Biologicals, Quebec) with or without seasonal TIV between 1 October 2009 and 31 January 2010 as determined by parent report and/or medical records. The A H1N1 2009 vaccine was egg-derived, formalin-inactivated, detergent split and had thimerosal present as a preservative. Each 0.25 mL dose contained 1.875 μg of hemagglutinin of the H1N12009 pandemic influenza virus vaccine which was mixed with an equal volume of adjuvant containing DL-alpha tocopherol (5.95 mg) and squalene (5.35 mg).

Children were excluded if they had a history of systemic hypersensitivity to hens' eggs or to any influenza vaccine, allergy to any component of the study vaccine, receipt of non-study TIV for 2010–2011, receipt of any live vaccine within 4 weeks or inactivated vaccine within one week of study entry or planned administration of any non-study vaccines during the study period, thrombocytopenia or any bleeding disorder that contraindicates intramuscular injection or blood collection, receipt of blood-derived products within the past 3 months, or participation in any other research study involving a non-approved drug or medical device. Temporary exclusion criteria were current febrile or other self-limiting moderate to severe illness, so that a subject could be immunized once the condition had resolved.

2.2. Vaccine

The TIV vaccine was Fluviral S/F manufactured by GSK (Laval) for the 2010–2011 season, containing the WHO-recommended antigens from H1N1, H3N2 and B viruses for the Northern Hemisphere [7] which were A/California/7/2009-like (H1N1), A/Perth/16/2009-like (H3N2) and B/Brisbane/60/2008-like (B/Victoria lineage) viruses.

This TIV is egg-derived, formalin-inactivated and detergent-split. Each 0.5 mL dose contains 15 μg of hemagglutinin of each strain along with traces of egg protein, formalin, and sodium deoxycholate detergent. The antigens are diluted in phosphate buffered saline solution. Thimerosal preservative is present in a concentration of 0.01%. No antibiotic is present in the vaccine. Vaccine was supplied in 10-dose (5.0 mL) vials. A single lot of vaccine was used.

Children 12–35 months of age received 0.25 mL and children 36 months to 59 months of age 0.50 mL intramuscularly. A 2 dose TIV schedule was used for children who had not received at least 1 age-appropriate dose of TIV in a previous season, regardless of the history of pandemic influenza vaccine receipt. The antigens for the Northern Hemisphere for the previous year (2009–2010) were A/Brisbane/59/2007(H1N1), A/Brisbane/10/2007(H3N2) and B/Brisbane/60/2008-like (B/Victoria lineage).

2.3. Study procedures

The protocol was developed in the spring of 2010 and approved by the Research Ethics Board at each participating institution, and by Health Canada in July and August. The study was conducted according to Good Clinical Practice. A parent/guardian provided informed, written consent for each subject. Recruitment of the first 50 participants began 7 Sept 2010 at the Halifax site. Day 2 safety data, expected to capture most events of interest, were reviewed by a Data Safety Monitoring Board (DSMB) and approval to begin enrolment at the other sites (Vancouver, Montreal, Calgary) given on 17 Sept. Public TIV programs in Canada began in early to mid October.

At the first visit, eligibility of the child to participate was determined by medical history and history-directed physical examination. A baseline blood sample (3–5 mL) was collected and the first vaccination given. Subjects were observed for 30 min after vaccine receipt. The parent/guardian was shown how to record any symptoms or signs of changes in health (including daily temperature measurements) that occurred daily during days 0–6 after each vaccination, using a memory aid and thermometer supplied for that purpose. Medication for discomfort or fever was permitted after vaccine receipt.

2.4. Safety observations

Parents/guardians made daily notes of any local and/or systemic symptoms in the 7 days after each vaccination, using a memory aid supplied for this purpose. To enhance safety monitoring, a pre-arranged phone call was made to the parent/guardian to inquire about significant health events in the ~24 h after TIV receipt, and a summary report on these observations was prepared for rapid reporting to public health. A second phone call to review the child's health status occurred at the end of the first week. A significant health event was defined as any solicited health event scored as severe or temperatures >38.5 °C axilla or any unsolicited health changes resulting in unscheduled visits to a health professional (physician, emergency department, hospital) or inability to conduct scheduled activities such as go to school/daycare/(for the parent) work or leaving home as planned. Safety data was collected for all changes in health between days 0 and 6 and only for significant health changes during days 7–21 after each vaccination. The