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Randomized evaluation of live attenuated vs. inactivated influenza vaccines in schools (RELATIVES) cluster randomized trial: Pilot results from a household surveillance study to assess direct and indirect protection from influenza vaccination

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ABSTRACT

Background: Children are key drivers of influenza transmission. Vaccinating school age children decreases influenza in the community.
Objective: To pilot-test the methods for a future trial to compare the direct and indirect benefits of inactivated influenza vaccine (IIV) vs. live attenuated influenza vaccine (LAIV) in preventing influenza infection.
Methods: During the 2013–14 influenza vaccination campaign, we piloted an open-label cluster randomized trial involving 10 elementary schools in Peterborough, Ontario, Canada. We randomized schools on a 1:1 basis to have students receive IIV or LAIV. We invited a subset of vaccinated students and their households to participate in a surveillance sub-study, which involved completing daily symptom diaries during influenza season and collecting mid-turbinate swabs from symptomatic individuals to detect influenza infection. The main outcome measure was confirmed influenza infection using a real-time reverse transcriptase polymerase chain reaction (PCR) assay.
Results: One hundred and nineteen households (166 students and 293 household members) participated. During 15 weeks of surveillance, we detected 22 episodes of PCR-confirmed influenza (21 influenza A/H1N1 and 1 influenza B). The incidence of influenza per 1000

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person-days was 1.24 (95% CI, 0.40–2.89) for IIV-vaccinated students, compared to 0.13 (95% CI, 0.003–0.72) for LAIV-vaccinated students; the incidence rate ratio was 0.10 (95% CI, 0.002–0.94). Similarly, the incidence of influenza per 1000 person-days was 1.33 (95% CI, 0.64–2.44) for IIV household members, compared to 0.47 (95% CI, 0.17–1.03) for LAIV household members; the incidence rate ratio was 0.36 (95% CI, 0.11–1.08). The overall incidence rate ratio (combining students and household members) was 0.27 (95% CI, 0.09–0.69).

Conclusions: Household surveillance involving participant monitoring and reporting of symptoms and self-collection of mid-turbinate swabs is feasible. A larger study is required to validate the suggestion that vaccinating children with LAIV might confer more protection against influenza for both children and their household contacts, compared to IIV.

Trial registration: ClinicalTrials.gov NCT01995851.

1. Introduction

School children drive influenza epidemics through virus transmission to their contacts [1–4]. Mathematical models and field research suggest that vaccinating school children provides indirect protection (herd immunity) to both household members and the community at large [5–9], thereby reducing the burden of influenza. However, influenza vaccine coverage in children is suboptimal for various reasons, including accessibility, competing demands, and fear of needles among children [10–12].

An alternative to injectable inactivated influenza vaccine (IIV) is the intranasal, live attenuated influenza vaccine (LAIV). LAIV was first approved for use in the United States in 2003 for individuals aged 5–49 years, and extended to those aged 2–49 years in 2007 [13]. In Canada, LAIV was approved for use in June 2010, and for the 2011–12 to 2013–14 influenza seasons Canada's National Advisory Committee on Immunization preferentially recommended it over IIV for healthy children aged 2–17 years based on efficacy, effectiveness, and immunogenicity [14–17]. However, the extent of indirect protection from LAIV for reducing the incidence of laboratory-confirmed influenza among household contacts has not yet been established.

In the fall of 2013, we piloted a cluster randomized trial to evaluate administering LAIV vs. IIV to children at school-based influenza immunization clinics. A cluster design was used because the intervention was at the level of the school. This paper describes a nested sub-study involving students who were vaccinated as part of the larger study. We conducted surveillance of the vaccinated students and their households for influenza infection in order to assess feasibility of study procedures and generate parameter estimates to inform a full-scale trial evaluating the direct and indirect benefits of LAIV.

2. Methods

We conducted an open-label cluster randomized trial involving 10 elementary schools within the geographic boundaries of the Peterborough County-City Public Health Unit (PCCHU) during the 2013–14 influenza vaccination campaign. PCCHU is the local public health department that serves a mixed urban-rural community 125 km northeast of Toronto, Ontario. Out of the 28 schools belonging to the Kawartha Pine Ridge District School Board, 10 agreed to participate. Using a standard computer pseudorandom number generator, researcher JAP randomized the schools on a 1:1 basis to having students between Junior Kindergarten (age 4) and Grade 8 (age 13) offered free LAIV (FluMist®) or IIV (Vaxigrip®) at PCCHU-organized school-based immunization clinics between 11 and 22 November 2013. Both vaccines contained A/California/7/2009 (H1N1) X-179A, A/Texas/50/2012 (H3N2) X-223A, and B/Massachusetts/2/2012 (Yamagata lineage) BX-51B viruses. Details are described elsewhere [18].

We invited 320 households (with 429 school-vaccinated students from 9 of the 10 schools to participate in this study). One IIV-assigned school, representing 11 households with 20 vaccinated students, was excluded from the study due to distance from the city of Peterborough and the related challenges of reaching them for follow-up in the winter. The study involved monitoring for acute respiratory symptoms among all household members and collecting specimens from symptomatic participants to test for influenza during the period of local influenza activity.

2.1. Recruitment

Between 6 December 2013 and 1 February 2014, research assistants attempted to contact each vaccinated student's parent(s) by telephone to participate. Repeated calls were made to those who could not be reached, until the end of the recruitment period. We limited recruitment from each school to a maximum of 25 households. A research assistant visited interested households to obtain written consent from each adult (aged ≥16 years) in the family and assent from each child younger than 16 years. Households were offered an incentive of a $25 Amazon.ca gift card per participant.

2.2. Study procedures

Once consent/assent was obtained for the household, a research assistant recorded baseline data from each household member, including demographics, risk factors for influenza complications, and current influenza vaccination status. We provided each household with either paper or electronic diaries (via a link to an Internet-based questionnaire) for recording daily symptoms, a digital thermometer, Copan flocked nasal swabs, and training on the collection of mid-turbinate swabs from oneself or other household members.

We instructed participating households to complete the daily diary to record whether any household member had acute respiratory symptoms, illness history (e.g., hospitalizations related to lower respiratory tract infections and pneumonia, physician visits for respiratory illness), and missed days of school or work due to acute respiratory infections. If any household member exhibited any one of cough, sore throat, or fever, or at least two other symptoms (runny nose, headache, sinus problems, muscle aches, fatigue/very tired, ear ache, ear infection, chills, and sneezing), they were to collect a mid-turbinate swab on themselves (or parents would swab children) as soon as symptoms appeared (within 48 h), and to call a research assistant to collect a second mid-turbinate swab. Thus there were typically two swabs per episode of illness, so that we could compare participant collection with research assistant collection. A participant was considered to have had a positive test if either of the two specimens was positive for influenza. A repeat swab was collected 7 days after the collection of the initial swab (indicating a new episode) if the individual had at least

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