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A multi-site feasibility study to assess fever and wheezing in children after influenza vaccines using text messaging

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ABSTRACT

Background: Using text messaging for vaccine safety monitoring, particularly for non-medically attended events, would be valuable for pandemic influenza and emergency vaccination program preparedness. We assessed the feasibility and acceptability of text messaging to evaluate fever and wheezing post-influenza vaccination in a prospective, observational, multi-site pediatric study.

Methods: Children aged 2–11 years old, with an emphasis on children with asthma, were recruited during the 2014–2015 influenza season from three community-based clinics in New York City, and during the 2014–2015 and 2015–2016 seasons from a private practice in Fall River, Massachusetts. Parents of enrolled children receiving quadrivalent live attenuated (LAIV4) or inactivated influenza vaccine (IIV4) replied to text messages assessing respiratory symptoms (day 3 and 7, then weekly through day 42), and temperature on the night of vaccination and the next seven nights (day 0–7). Missing data were collected via diary (day 0–7 only) and phone. Phone confirmation was obtained for both presence and absence of respiratory symptoms. Reporting rates, fever ($T \geq 100.4$ °F) frequency, proportion of wheezing and/or chest tightness reports captured via text message versus all sources (text, phone, diary, electronic health record) and parental satisfaction were assessed.

Results: Across both seasons, 266 children were analyzed; 49.2% with asthma. Parental text message response rates were high (>70%) across sites. Overall, fever frequency was low (day 0–2: 4.1% [95% confidence interval (CI) 2.3–7.4%]; d3–7: 6.7% [95% CI 4.1–10.8%]). A third (39.2%) of parents reported a respiratory problem in their child, primarily cough. Most (88.2%) of the 52 wheezing and/or chest tightness reports were by text message. Most (88.1%) participants preferred text messaging over paper reporting.

Conclusions: Text messaging can provide information about pediatric post-vaccination fever and wheezing and was viewed positively by parents. It could be a helpful tool for rapid vaccine safety monitoring during a pandemic or other emergency vaccination program.

Conclusions: Trial registration: clinicaltrials.gov Identifier: NCT02295007.

1. Introduction

The Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination for all individuals ≥6 months-old [1]. Understanding influenza vaccine safety is important for annual vaccination programs and pandemic preparedness. Influenza vaccine is the only vaccine recommended annually, with formulations often changing yearly [2]. While seasonal vaccine safety patterns are usually similar, unexpected adverse events may arise. For example, the 2010–2011 trivalent inactivated influenza vaccine

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was associated with an increased febrile seizure risk in young children [3].

Although following a large number of vaccinated people prospectively for post-licensure vaccine-associated adverse events can be labor-intensive and expensive, we and others have successfully used text messaging- a scalable, low-cost method- for this purpose [4–8]. Currently, 95% of American adults have a cell phone [9]. Cell phone use is thought to be higher in harder-to-reach low-income populations [10] that may not be included in vaccine safety monitoring programs relying on information from managed care organizations [11]. Text messaging is particularly useful for monitoring of non-medically attended events, such as fever, since it allows patients or caregivers to report symptoms directly. This may be important in an influenza pandemic when information may need to be gathered rapidly and simultaneously from large numbers of vaccinated people nationally, but visits to medical facilities may be limited. Some important issues remain in the use of text messaging for monitoring vaccine-associated adverse events. First, adverse events may occur several weeks post-vaccination, but previous pediatric studies have focused primarily on the more immediate 7–10 days post-vaccination. Second, unlike in Australia [12], text messaging has not been used to date in the United States to assess vaccine safety outcomes at multiple sites, but multi-site vaccine safety monitoring would have value for pandemic and emergency vaccination program preparedness. Third, although wheezing is not considered a safety concern after IIV, accuracy of text messaging to capture respiratory events may be pertinent for monitoring safety of live attenuated influenza vaccination (LAIV) [13]. During our study period, ACIP recommended LAIV preferentially for healthy 2- through 8-year olds for the 2014–15 season; for 2015–16 season there was no preferential recommendation, but LAIV was an acceptable option for use in healthy children [14,15].

This study's primary goal was to assess feasibility and acceptability of text messaging to assess wheezing prospectively from day 0 (vaccination day) through day 42 post-vaccination in children aged 2–11 years-old receiving quadrivalent live attenuated (LAIV4) or inactivated (IIV4) influenza vaccine. We hypothesized that (1) at least 80% of wheezing symptoms reported via text message would be verified by phone interview, in those able to be reached, and medical record review for those with a visit; (2) response rates to text message queries regarding wheezing symptoms would be higher on days 3 and 7 post-vaccination than on days 14–42; and (3) at least 80% of parents would have a high level of satisfaction with using text messaging to report wheezing occurring post-vaccination. A secondary objective was to assess feasibility of monitoring post-vaccination wheezing and fever using text messaging at multiple sites. We hypothesized that text message response rates would not differ by more than 10 percentage points between sites.

2. Materials and methods

This prospective observational study was conducted during the 2014–2015 (Year 1) and 2015–2016 (Year 2) influenza seasons, in collaboration with the Centers for Disease Control and Prevention (CDC). During the 2014–2015 season, children were recruited from three community-based clinics affiliated with New York-Presbyterian Hospital/Columbia University Medical Center (CUMC) in New York City. These sites serve a primarily Latino, publicly-insured population and share an electronic health record (EHR) system with the hospital. During the 2014–2015 and 2015–2016 seasons, children were recruited from a private general pediatric practice in Fall River, Massachusetts affiliated with Boston Medical Center (BMC) that has its own EHR system. Each child also had a parent or guardian participate in the study. All text messages for both sites were sent from a centralized program to the parent (or guardian) participating in the study. Vaccination decisions were made by the patients' health care provider and caregivers, and all influenza vaccines administered were the quadrivalent forms. The influenza vaccine strain composition differed in the two seasons for both an A and B strain. CUMC and BMC's Institutional Review Boards (IRB) approved the study; CDC relied on the CUMC approval.

Children were eligible for enrollment if they (1) were 2–11 years-old, (2) were receiving their first or second influenza dose of that season, (3) their parent had a cell phone with text messaging capabilities, and (4) their parent spoke English or Spanish at CUMC sites or English at the BMC site. Exclusion criteria included (1) any chronic medical condition considered a contraindication or precaution for LAIV (with the exception of asthma/wheezing history) [14], (2) current/recent (<2 weeks) asthma exacerbation, (3) oral or other systemic steroid use in the preceding 2 weeks, (4) temperature (T) $\geq$100.4 °F at vaccination, (5) antipyretic administration within 6-hours pre-vaccination or stated intent to use prophylactic antipyretics, (6) parental inability to read or send text messages, and (7) sibling or child already enrolled in either season. Receipt of other vaccines was not an exclusion criterion.

2.1. Study procedures

Parents provided consent and completed an intake form, including demographic information and parent-reported child history of asthma/reactive airway disease (RAD)/recurrent wheezing. Study staff reviewed text message procedures. Parents received and were trained with a temporal artery thermometer [16], and were given a paper diary in a pre-addressed/pre-stamped envelope to return after the first 7-day observation period.

Parents were asked to take their child's temperature each evening from the day of vaccination (day 0) through the next 7 days, or at any time during those days if the child felt febrile. Parents were sent an interactive text message (in English or Spanish, based on participant language choice) nightly, asking the highest temperature, time taken, name and time of any antipyretics given, and care sought. Respiratory questions were sent on days 3, 7, 14, 21, 28, 35 and 42 (none, wheeze, cough, and/or chest tightness). If respiratory symptoms were reported, additional information was prompted including medications and care visits. Unanswered text messages were re-sent 20 minutes later to prompt a response.

The centralized text messaging program had built-in messages sent back for an unexpected reply (*e.g.* T < 95 °F or >106 °F degrees) with instructions to correct the error. Study staff reviewed messages daily initiating contact with non-responders to collect missing data, and with responders reporting respiratory symptoms to confirm them. Parents that reported either no respiratory symptoms on d3–d21 texts or no symptoms some days and failed to report other days, were called soon after d21 to confirm the child had no symptoms. A telephone exit survey was administered to all participants after the last text message was sent on d42 to confirm absence or presence of respiratory symptoms occurring on d28–d42 and assess parental satisfaction.

Vaccinations given at enrollment and during d1–d42 post-vaccination, as well as all healthcare visits (ambulatory care, emergency department and hospital) between d0–d42 post-vaccination, were abstracted from the EHR. Chart documentation of history of asthma/RAD/recurrent wheezing, as well as associated medications, were abstracted. Abstracted data were used by two separate investigators per site to adjudicate whether the child had chart documentation of asthma exacerbation and/or asthma medication prescription documented within 12 months before enrollment (i.e., recent history), or asthma/RAD/ recurrent wheezing diagnosis not

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