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Influenza vaccines effectiveness 2013–14 through 2015–16, a test-negative study in children

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ABSTRACT

Background: Trivalent inactivated and live attenuated influenza vaccines (IIV3 and LAIV3) have been reformulated with an extra B strain (IIV4 and LAIV4). They were licensed based on immunogenicity and their effectiveness (VE) still must be empirically tested.
Methods: Children 1–17 years tested for influenza during 2013–16 were included and their immunization status verified. They were considered vaccinated if received ≥1 dose of an influenza vaccine ≥10 days before evaluated for a respiratory episode. Age-groups were classified as 1–4 years or 5–17 years. VE was estimated by comparing vaccination status of influenza-positive versus influenza-negative cases.
Results: 6779 children were enrolled in the three seasons. Overall, 27.2% received an influenza vaccine (87.1% IIV3 or IIV4 and 12.9% LAIV4), and 15.6% tested positive for influenza (77.9% A). IIV3 was predominantly used in 2013–14 and IIV4 in 2014–15 and 2015–16. IIV3 and IIV4 had comparable VE over the three seasons (60%, 57% and 53%) and performed similarly against influenza A and B and both age-groups. LAIV4 performed poorly for influenza A (15%, 37% and 48%) but better for influenza B (100%, 56% and 100%), especially among children 5–17 years of age with VE = 100% (95%CI: 55, 100).
Conclusions: Influenza vaccination showed modest but consistent effectiveness over the years. The switch from IIV3 to IIV4 did not affect VE. LAIV4 did not perform as well as IIVs, yet it improved over the years and was particularly good protecting older children against influenza B. These results emphasize the regional nature of influenza and the need for local surveillance.

1. Introduction

Influenza is one of the most common vaccine preventable diseases still endemic in the United States causing approximately 200,000 hospitalizations and 3000–49,000 deaths every year [1]. The best mode of preventing influenza is through vaccination. However, due to annual antigenic variability the vaccine must be re-formulated and re-administered every year. Also, because of multiplicity in circulating strains it must be a multicomponent vaccine. Until recently, inactivated influenza vaccines (IIVs) contained three strains (IIV3): two A (one representative of H1N1 and one of H3N2) and one B (representative of one of the two B virus lineages). More recently, IIVs have been reformulated to include four components (IIV4): the same three of IIV3 plus one extra B strain (representative of the other B virus lineage) [2]. IIV4 was approved by the US Food and Drugs Administration in 2013 based on safety and immunogenicity data [3]. Similarly, the live attenuated influenza vaccine (LAIV) was first licensed as a three-component vaccine (LAIV3) in 2003 and fully replaced by a four-component vaccine (LAIV4) for the 2013–14 season; the four components in LAIV4 are the same as in IIV4. Mathematical projections have suggested that had a quadrivalent instead of a trivalent influenza vaccine been utilized in the U.S. for the 10-year period 1999–2009 it could have further reduced annual cases, hospitalizations and deaths by 2200–970,000, 14–8200 and 1–485, respectively [4]; this public health impact has not been empirically tested, though.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CI, confidence interval; IIV, inactivated influenza vaccine; IIV3, trivalent IIV; IIV4, quadrivalent IIV; LAIV, live attenuated influenza vaccine; LAIV3, trivalent LAIV; LAIV4, quadrivalent LAIV; LINKS, Louisiana Immunization Network for Kids Statewide; OR, odds ratio; VE, vaccine effectiveness.

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Because of constant antigenic changes of influenza strains and recent reformulations of influenza vaccines, it is important to have ongoing surveillance to monitor their effectiveness (VE). One such surveillance system is the US Influenza Vaccine Effectiveness Network sponsored by the Centers for Disease Control and Prevention (CDC, Atlanta, GA) and consisting of five study sites across the US. Their data has been instrumental to track influenza activity, estimate annual VE and support recommendations on immunization. In their work, CDC employs a test-negative design. The test-negative has emerged as an alternative to cohort or case-control designs; it enrolls cases tested for influenza and compares rates of vaccination for those testing positive versus those testing negative to provide an estimate of VE against medically attended disease [5]. The test-negative design is convenient and has been found valid under a wide range of assumptions [6].

Due to local variability in population characteristics and influenza activity it is important for individual regions to produce their own data. Given that in 2013 our hospital improved its diagnostic ability to detect influenza by the addition of a nucleic acid amplification test, the present study aimed to review our experience since 2013–2016 and using a test-negative design estimate VE of the different vaccine preparations; we were especially interested in the comparative VE of IIV3 and IIV4, as well as IIVs (IIV3 and IIV4 combined) compared to LAIV4.

2. Methods

The study was approved and oversight provided by the Institutional Review Board of Louisiana State University Health Sciences Center and Children's Hospital New Orleans, Louisiana. A Waiver of Informed Consent was requested and granted.

2.1. Data collection

The hospital clinical laboratory provided a list of children (inpatients and outpatients) who had a respiratory specimen submitted between July 1st 2013 and June 30th 2016. The list contained name of the patient, date of birth, date of collection of the specimen, and influenza test result. Our institutional protocol recommends that suspected cases of influenza should first be tested with a rapid influenza test (RIT; Binax NOW® Influenza A&B Card, Alere Scarborough, Inc, Maine) and, if negative, then further tested with a multiplex PCR system (FilmArray® Respiratory Panel, Biomérieux, France). As reported by the manufacturers, the RIT has a sensitivity of 81% for influenza A and 65% for influenza B, and specificity of 97% and 100%, respectively [7], and the FilmArray® PCR has sensitivity of 90% and specificity of 99.6–100% for influenza A or B [8]. The RIT identifies Influenza as A or B (no subtypes), while the FimArray® PCR system identifies influenza as A and its subtypes (A/H1, A/H3, A/H1-2009) or B (no subtypes). The list was restricted to the time when influenza was circulating. The start and end of influenza season was defined by the first week when the percent of positive tests consistently exceeded or declined below 5%, respectively; the influenza A and influenza B season were defined similarly. Cases were circumscribed to ages 1–17 years; children 6–11 months of age when seen were excluded since their period of opportunity to receive the vaccine may have been shorter than for older children. Tests performed in patients with conditions or treatments that may affect vaccine response (i.e., immunocompromised) were excluded; tests originated in patients admitted >72 h (i.e., hospital-acquired) were also excluded. Repeat specimens from the same patient within four weeks were considered likely part of the same event and counted as one specimen.

2.2. Immunization status

Using name and date of birth, the patient's record was sought in the publicly available Louisiana Immunization Network for Kids Statewide (LINKS) [9]. LINKS is part of the federally sponsored Immunization Information System with a reported participation ≥95% for children aged <6 years [10]. Receipt of an influenza vaccine before the respiratory episode was verified recording the type of vaccine utilized: IIV3, IIV4 or LAIV4. Cases not found in LINKS or cases in which the type of vaccine was not clear or marked as "unspecified" were excluded.

2.3. Data analysis

The list of cases was divided into three influenza seasons (2013–14, 2014–15 and 2015–16). Test results were classified into influenza-positive or influenza-negative; influenza-positive cases were further classified into influenza A or influenza B. The immunization status of each patient was classified as none, IIV3, IIV4, IIVs (either IIV3 or IIV4) or LAIV4. To be valid, at least 1 vaccine dose should have been administered 10 days before the respiratory episode; otherwise cases were considered unvaccinated. Analyses for IIVs included the full group 1–17 years of age; analyses for LAIV4 included ages 2–17 years since LAIV is approved for children 2 years and older only. Age-groups were classified as 1–4 years (younger children) or 5–17 years (older children) for IIVs, or 2–4 years and 5–17 years for LAIV4.

Vaccine effectiveness (VE) was estimated with a test-negative design comparing vaccination status of influenza-positive cases to vaccination status of influenza-negative cases with the formula $VE = (1 - OR) * 100\%$, where OR = (odds of vaccination among influenza-positive cases)/(odds of vaccination among influenza-negative cases) [11]. OR with corresponding 95% confidence limits (CI) was calculated by logistic regression (Epi Info™ 7, Centers for Disease Control and Prevention, Atlanta, GA): influenza-result (positive or negative) was the dependent variable, vaccine administered the independent variable, and age (in months) and week of enrollment the co-variables. To estimate VE against any influenza (A or B), cases seen during the entire influenza season were included; to estimate VE against influenza A or B specifically, only cases seen during the period when influenza A or B, respectively, were circulating were included in the analysis. For cases with a "0" in the OR numerator (i.e., no recipient of that specific vaccine among influenza-positive cases) logistic regression failed to calculate an upper boundary of OR (i.e., lower boundary of VE); in those cases OR was calculated with Statcalc (Epi Info™ 7) with Cornfield's 95%CI. The relative VE of two vaccine types (e.g., IIV4 vs IIV3 or LAIV4 vs IIVs) was estimated by comparing the odds of testing influenza-positive among those who received one vaccine versus the other, adjusted for age and calendar time, and expressed as OR and 95%CI. Proportions (e.g., percent subjects vaccinated or percent subjects infected) were compared with chi-square Yate's corrected.

3. Results

3.1. Study population

Three sequential influenza seasons were included; their characteristics are shown in Table 1. The first two seasons started early (November and October), were long (lasting 5 and 8 months) and with a relatively clear demarcation in the circulation of influenza A and B. The third season started late (February), was short (2.5 months) and had significant overlap in the circulation of influenza A and B. Of 6779 cases included, 1059 (15.6%) tested