Brief report

Efficacy of live attenuated influenza vaccine against influenza illness in children as a function of illness severity

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A R T I C L E   I N F O
Article history:
Received 5 March 2014
Received in revised form 9 July 2014
Accepted 31 July 2014
Available online 12 August 2014

Keywords:
Influenza
Disease severity
Live attenuated influenza vaccine

A B S T R A C T
A recent study of inactivated influenza vaccine (IIV) in children aged 3–8 years demonstrated higher efficacy against moderate/severe influenza. A meta-analysis of all previous published randomized clinical trials of live attenuated influenza vaccine (LAIV) that collected information on illness severity in children aged 24–71 months was conducted. Moderate/severe influenza was defined as fever >39 °C, acute otitis media, or lower respiratory tract illness; other cases were classified as milder influenza. LAIV efficacy versus placebo was 95.4% [95% confidence interval: 88.5, 98.1] (year 1) and 88.5% [77.4, 94.9] (year 2) against moderate/severe influenza and 91.4% [77.9, 96.7] (year 1) and 84.2% [56.7, 94.3] (year 2) against milder influenza. The relative efficacy of LAIV versus IIV was 52.2% [31.6, 66.6] for moderate/severe influenza and 45.0% [28.6, 57.5] for milder influenza. Efficacy against all influenza illnesses, regardless of severity, is critical to prevent influenza illness and transmission in the community.
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1. Introduction
Due to the high rate of influenza infection in children and the availability of safe and effective vaccines [1–5], the US Centers for Disease Control and Prevention recommends influenza vaccination for all children 6 months and older for their own protection [6]. A study by Public Health England researchers that also took into account the role of children in the transmission of influenza concluded that the most efficient use of vaccines to reduce overall influenza morbidity and mortality in England and Wales is to target children in addition to older adults [7].

The efficacy of influenza vaccines has traditionally been assessed against symptomatic laboratory-confirmed influenza illnesses without specific consideration of disease severity. However, a recently published efficacy study of inactivated influenza vaccine (IIV) versus placebo in children 3–8 years of age evaluated vaccine efficacy as a function of influenza severity [8]. The per-protocol efficacy of IIV was 55% against all laboratory-confirmed cases of influenza. Efficacy was higher (74%) against moderate/severe cases due to increased efficacy against moderate/severe influenza A disease; efficacy was lower (42%; author personal communication) against milder influenza B and influenza A illnesses. Moderate/severe illnesses were those associated with the presence of fever >39 °C, acute otitis media, or lower respiratory tract illness.

The efficacy of live attenuated influenza virus (LAIV) in children has been documented in several clinical trials [9], but has not been assessed with regard to disease severity. The purpose of this study was to evaluate the efficacy of LAIV against moderate/severe and milder laboratory-confirmed influenza in children >24 months of age.

2. Materials and methods

2.1. Clinical studies

All randomized clinical trials that evaluated the efficacy of LAIV in children aged 2–17 years were reviewed: two previously published prospective, double-blind, randomized clinical trials comparing the efficacy of LAIV versus placebo or IIV in children collected data regarding influenza illness severity [10–12].

Study 1 was a two-year placebo-controlled study conducted in the United States in healthy children 15–71 months of age [11,12]. Subjects were randomly assigned in a 2:1 ratio to receive LAIV or placebo. In year 1, subjects received LAIV or placebo as a single dose or 2 doses administered approximately 60 days apart [11]. In year 2, subjects received 1 dose of LAIV or placebo according to the randomization schedule in year 1 [12].

http://dx.doi.org/10.1016/j.vaccine.2014.07.097
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Study 2 was a one-year IIV-controlled study. Healthy children 6–59 months of age in the United States, Europe, and Asia were randomly assigned in a 1:1 ratio to receive either LAIV or IIV [10]. Vaccine-naive children were administered two doses of vaccine within a 42-day period; children who had been vaccinated previously received one dose.

LAIV consisted of 10^6.5–7.5 median tissue culture infectious doses (TCID50) or fluorescent focus units of each of the three influenza strains (A/H1N1, A/H3N2, and B) contained in the vaccine. The IIV-controlled study used IIV manufactured by Aventis Pasteur in the corresponding region; children 6 months to <36 months of age received 0.25 ml per dose (7.5 μg of each hemagglutinin) while children ≥36 months of age received 0.5 ml per dose (15 μg of each hemagglutinin). The characteristics of all vaccines have been previously reported [10–12]. Both studies were conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Efficacy endpoints

Parents or guardians recorded daily temperatures and signs or symptoms of respiratory illness and were instructed to promptly notify study personnel if their child developed qualifying symptoms. They were also contacted every 7–10 days throughout the influenza season.

Nasal swabs were collected if a child had ≥1 of the following: acute otitis media (suspected or diagnosed), fever, pneumonia, pulmonary congestion, shortness of breath, or wheezing, or ≥2 of the following symptoms concurrently: chills, cough, decreased activity, headache, irritability, muscle aches, pharyngitis, rhinorrhea, or vomiting. Central laboratories evaluated nasal swabs for the presence of influenza virus by viral culture; wild-type serotypes were identified using antigenic methods.

Laboratory-confirmed cases of influenza were classified as moderate/severe influenza if there was any documentation of fever >39 °C, acute otitis media, or lower respiratory tract illness (defined as healthcare provider-confirmed shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, or cough). All other cases were classified as milder influenza.

2.3. Statistical analysis

All children ≥24 months of age were retained in this post hoc analysis. Efficacy was calculated as one minus the relative risk of laboratory-confirmed influenza regardless of antigenic match with LAIV versus placebo or IIV. Efficacy was evaluated first against moderate/severe cases of influenza in all children, then against mild cases of influenza only. The 95% CIs of the vaccine efficacy point estimates were obtained by a log-binomial regression. Results from the two studies were not combined because study 1 assessed LAIV efficacy versus placebo, whereas study 2 assessed LAIV efficacy versus IIV.

3. Results

A total of 1330 children ≥24 months of age in year 1 (LAIV, n = 897; placebo, n = 433) and 1358 children in year 2 (LAIV, n = 917; placebo, n = 441) were enrolled in study 1. The attack rates of moderate/severe influenza were 0.6% (5/897) in year 1 and 1.1% (10/917) in year 2 in the LAIV group versus 12.0% (52/433) in year 1 and 9.5% (42/441) in year 2 in the placebo group, resulting in efficacy estimates of 95.4% (95% CI: 88.5, 98.1) in year 1 and 88.5% (77.4, 94.9) in year 2 (Figs. 1A and 1B). The attack rates of mild influenza were 0.6% (5/892) in year 1 and 0.6% (5/907) in year 2 in the LAIV group versus 6.6% (25/381) in year 1 and 3.6% (14/399) in year 2 in the placebo group, resulting in efficacy estimates of 91.4% (77.9, 96.7) and 84.2% (56.7, 94.3) in year 1 and year 2, respectively (Figs. 1A and 1B). In year 1, both A/H3N2 and B strains circulated. Efficacy against moderate/severe influenza for A/H3N2 and B strains was 95.7% (86.5, 99.2) and 95.8% (83.0, 99.5), respectively. Efficacy against mild influenza for A/H3N2 and B strains was 94.3% (76.1, 99.4) and 83.9% (35.5, 97.2), respectively.

Study 2 enrolled a total of 4166 children ≥24 months of age (LAIV, n = 2083; placebo, n = 2083). The attack rate of moderate/severe influenza was 2.1% (43/2083) in the LAIV group versus 4.3% (90/2083) in the IIV group, resulting in a relative efficacy of LAIV compared with IIV of 52.2% (31.6, 66.6). The attack rate of mild

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Fig. 1. Efficacy of LAIV compared with placebo. (A) Study 1, year 1, moderate/severe influenza illness; (B) Study 1, year 2, moderate/severe and mild influenza illness; (C) Study 2, relative efficacy of LAIV compared with IIV. IIV = inactivated influenza vaccine; LAIV = live attenuated influenza vaccine.
influenza, after exclusion of moderate or severe cases, was 4.1% (84/2040) in the LAIV group versus 7.5% (149/1993) in the placebo group, resulting in a relative efficacy of 45.0% (28.6, 57.5) (Fig. 1C). Efficacy against moderate/severe influenza for A/H1N1, A/H3N2, and B was 100% (−91.1, 100), 80.9 (60.5, 91.7), and 10.3 (−45.4, 44.8), respectively. Efficacy against mild influenza for A/H1N1, A/H3N2, and B was 91.7% (66.4, 99.0), 59.1% (35.1, 74.9), and 13.6% (−25.0, 40.5).

4. Discussion

Children are considered a priority group for vaccination because of the high burden of influenza disease among children and the availability of safe and effective vaccines. Vaccinating children against influenza also can indirectly protect other age groups against influenza. Public health agencies promote vaccination against influenza in children because they have been identified as the main spreaders of influenza infection [7]. From this perspective, it is important to prevent any influenza case, independent of disease severity. To best characterize a vaccine’s effect on influenza transmission, influenza vaccine efficacy should be assessed against all shedding influenza infections, whether severe or mild, symptomatic or not [13].

Although several clinical trials have documented the efficacy of LAIV in children [9], this study is the first evaluation of LAIV efficacy as a function of disease severity. LAIV was efficacious against moderate/severe influenza and against milder influenza. LAIV was also significantly more efficacious than IV for influenza A disease of all severity levels. The lack of LAIV superiority relative to IV for influenza B in the current analysis may be due to the fact that a significant proportion of influenza B cases were due to antigenic variants. Two other IV-controlled studies of LAIV in children demonstrated LAIV superiority against matched B strains [14,15]; however, neither of these studies collected data on disease severity.

Together with the recent study demonstrating high levels of IV efficacy only against moderate/severe influenza A disease, the results of this analysis show that LAIV provides children with a high degree of protection against influenza A and B illness of all severity levels and thus should be effective in interrupting influenza transmission by children in the community. These differences in the efficacy of IV and LAIV in children may be due to the differential mechanisms of action of the two vaccines, with LAIV providing a robust mucosal immune responses and IV providing a predominantly systemic response; a more robust mucosal immune response could be more effective against more mild infections [16–18].

A limitation of this analysis is that we could not investigate vaccine efficacy against asymptomatic influenza infections. However, LAIV efficacy estimates remained stable for moderate/severe and mild influenza illness; the point estimates for efficacy against mild influenza were always contained within the 95% confidence intervals of the efficacy estimates against moderate/severe influenza. These results also suggest that LAIV might also be similarly efficacious against asymptomatic influenza infections. In summary, LAIV provided consistently high efficacy against moderate/severe and milder influenza illness compared with placebo in children >24 months of age. It also was consistently more efficacious than IV. Efficacy against all influenza illnesses, regardless of severity, is critical to prevent influenza illness and transmission in the community.

Acknowledgments

Contributors: Study concept and design was contributed by Dr. Ambrose. Acquisition of data was contributed by Drs. Ambrose, Belshe, and Wu. All the authors contributed to analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. The statistical analysis was contributed by Dr. Wu. All authors have seen and approved the final manuscript for submission.

Financial disclosures: Drs. Ambrose and Caspard are employees of AstraZeneca, the parent company of MedImmune, Gaithersburg, MD and may hold stock or stock options. Dr. Wu was an employee of MedImmune at time of analysis. Dr. Belshe has received research support from MedImmune and served as a consultant for and served on speakers’ bureaus for MedImmune and Merck. Fundingsupport: This research was sponsored by MedImmune.

Role of the sponsor: Some authors are employees of MedImmune and contributed to the design of the study, the analysis and interpretation of the data, and in reviewing and approving the manuscript. Additional contributions: Editorial assistance was provided by Susan E. DeRocco, Ph.D. and John E. Fincke, Ph.D. of Complete Healthcare Communications, Inc. (Chadds Ford, PA) and funded by MedImmune.

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