Vaccine 27 (2009) 1101–1110

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials

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ARTICLE INFO

Article history:
Received 26 June 2008
Received in revised form
21 November 2008
Accepted 26 November 2008
Available online 16 December 2008

Keywords:
Influenza vaccines
Live attenuated influenza vaccine (LAIV)
Meta-analysis
Efficacy
Children

ABSTRACT

Nine randomized clinical trials, including approximately 25,000 children aged 6–71 months and 2000 children aged 6–17 years, have evaluated the efficacy of live attenuated influenza vaccine (LAIV) against culture-confirmed influenza as compared to placebo or trivalent inactivated vaccine (TIV). We conducted meta-analyses, based on Mantel–Haenszel relative risks from fixed effect models, to provide an estimate of vaccine efficacy (VE). Relative to placebo, year 1 VE for two doses in vaccine-naïve young children was 77% (95% CI: 72%, 80%; $P < 0.001$) against antigenically similar strains and 72% against strains regardless of antigenic similarity. Efficacy was 85%, 76%, and 73% against antigenically similar A/H1N1, A/H3N2, and B, respectively. Year 1 VE of one dose against antigenically similar strains in vaccine-naive children was 60%; efficacy of one dose in previously vaccinated children in year 2 of the various studies was 87%. In head-to-head trials comparing two doses of TIV and LAIV, vaccine-naïve children who received two doses of LAIV experienced 46% fewer cases of influenza illness caused by antigenically similar strains. Similarly, for studies including older children who had been previously vaccinated, those receiving one LAIV dose experienced 35% fewer cases of influenza illness than those receiving one TIV dose. LAIV showed high VE versus placebo with no evidence of difference by age or by circulating subtype. In these studies, LAIV was more effective than TIV.

1. Introduction

Influenza virus causes significant morbidity and mortality worldwide [1–4], and annual influenza epidemics confer a heavy burden on health care systems [2,4–6]. Although children are among the most susceptible to influenza infection and are most likely to transmit the illness to others [2,6–10], many children do not receive influenza vaccination [8,11,12]. Moreover, most vaccine-naive children younger than 9 years of age who do receive vaccination receive only one dose rather than the recommended two-dose regimen [8,11,13].

An intranasal cold-adapted, live attenuated influenza virus vaccine [LAIV; FluMist® (Influenza Virus Vaccine Live, Intranasal); MedImmune, Gaithersburg, MD, USA] was first approved for use in the United States in 2003. In September 2007, the US Food and Drug Administration expanded the indication for use in individuals 2–49 years of age, from the previous 5–49-year indication. Several pediatric studies have characterized the safety and efficacy of LAIV in children, and the vaccine was shown to be efficacious in each of these studies [14–23] (Tables 1 and 2). Performing meta-analyses on clinically important subsets of the population of children evaluated in these studies provides more precise estimates of the efficacy of the LAIV vaccine than does reliance on a single study. Previous meta-analyses of LAIV efficacy [24–27] included data from several investigational LAIV formulations and did not include data from several recently published studies. The meta-analyses conducted here focus solely on data for the LAIV that has been approved for use in the United States (FluMist). We summarize data comparing the efficacy of LAIV with either trivalent inactivated influenza vaccine (TIV) or placebo.

2. Materials and methods

2.1. Studies used in the meta-analyses

Wyeth Vaccines Research (Pearl River, NY, USA) and MedImmune have conducted nine randomized, double-blind, controlled trials evaluating the efficacy of LAIV against culture-confirmed

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doi:10.1016/j.vaccine.2008.11.093

Table 1
Studies comparing LAIV with placebo included in meta-analyses.

Study period	*Population studied* countries	Age range (months)	Treatment group (doses, *n*)[a]	*n*[b]	Vaccine strains	Circulating strains
AV006[14,15] Year 1: August 1996 to April 1997	*Healthy children, influenza vaccine-naïve (year 1)* United States	≥15 to ≤71	LAIV (2), placebo (2)	881, 433	Year 1: A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like	Year 1: A/Wuhan/359/95-like (H3N2)[c], B/Harbin/7/94-like[c]
Year 2: September 1997 to May 1998			LAIV (1), placebo (1)	189, 99	Year 2: A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95 (Nanchang-like) (H3N2), B/Harbin/7/94-like	Year 2: A/Sydney/5/97 (H3N2), A/Wuhan/359/95-like (H3N2)[c], B/Harbin/7/94-like[c]
D153-P501[16] Year 1: September 2000 to October 2001	*Healthy children, influenza vaccine-naïve (year 1)* China, Hong Kong, India, Malaysia, Philippines, Singapore, Taiwan, Thailand	≥12 to <36	LAIV (2), placebo (2)	1900, 1274	Year 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	Year 1: A/Hawaii/15/01-like (H1N1), A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/22/01-like, B/Hong Kong/330/01-like[c], B/Hong Kong/1351/02-like[c], B/Sichuan/379/99-like[c], B/Victoria/504/00-like[c]
Year 2: November 2001 to October 2002					Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	Year 2: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Brisbane/32/02-like, B/Hong Kong/330/01-like[c], B/Hong Kong/1351/02-like[c], B/Shizuoka/15/01-like, B/Sichuan/379/99-like[c], B/Victoria/504/00-like[c], B/Yamanshi/166/98-like
D153-P502[17] Year 1: October 2000 to May 2001	*Healthy children attending day care, influenza vaccine-naïve (year 1)* Belgium, Finland, Israel, Spain, United Kingdom	≥6 to <36	LAIV (2), placebo (2)	1059, 725	Year 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	Year 1: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Sichuan/379/99-like
Year 2: December 2001 to May 2002					Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Year 2: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like, B/Victoria/504/00-like
D153-P504[18] Year 1: April 2001 to November 2001	*Healthy children, influenza vaccine-naïve (year 1)* South Africa, Brazil, Argentina	≥6 to <36	LAIV (2), placebo (1 or 2)[d]	1064, 1069	Year 1: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	Year 1: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Victoria/504/00-like[c], B/Yamanashi/166/98-like[c]
Year 2: March 2002 to November 2002			LAIV (1), placebo (1 or 2)[d]	1067, 1069	Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Year 2: A/Moscow/10/99-like (H3N2), A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like, B/Shenzhen/654/99-like, B/Sichuan/379/99-like, B/Victoria/504/00-like[c], B/Yamanahashi/166/98-like[c]