Relative Efficacy of Live Attenuated and Inactivated Influenza Vaccines in Children as a Function of Time Postvaccination

Christopher S. Ambrose, MD,[1] Xionghua Wu, PhD,[1] Robert B. Belshe, MD[2]

[1]MedImmune LLC, Gaithersburg, MD; [2]St. Louis University School of Medicine, St. Louis, MO

Introduction

- In the United States, all children 6 months through 18 years of age are recommended to be vaccinated annually against influenza.[1]
- Live attenuated influenza vaccine (LAIV) is approved in eligible children 2 years of age and older; trivalent inactivated influenza vaccine (TIV) formulations are approved for children as young as 6 months.[1]
- Three large, prospective, randomized studies compared the safety and efficacy of LAIV and TIV in children 6 months to 17 years of age. In these studies, LAIV recipients had 35%–53% fewer cases of influenza illness caused by antigenically similar strains compared with TIV recipients, with comparable safety among children 2 years of age and older.[2-4]
  - In one study among children 6–23 months of age, an increased rate of wheezing through 6 weeks after vaccination was associated with LAIV (5.9% LAIV vs 3.8% TIV, *P*=0.002); however, no increase was observed among children 24–59 months of age.[3]
- Increasing numbers of children are vaccinated against influenza in the United States in August and September,[5,6] a period much earlier in the year than vaccine efficacy trials.
- Early vaccination has been recommended by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics.[1,7]
  - 2009–2010 Centers for Disease Control and Prevention vaccine information statements for seasonal LAIV and TIV state that "protection lasts up to a year."[8,9]
- Previous analyses examined the impact of time on the efficacy of LAIV in young children compared with placebo, demonstrating comparable efficacy through 12 months postvaccination.[10,11]
- Although studies have described TIV-induced immunity in children at 4–12 months postvaccination,[12-16] few, if any, studies have described the impact of time on the efficacy of TIV against laboratory-confirmed wild-type influenza illness in children.

Objective

- To examine the relative efficacy of LAIV and TIV over time postvaccination

Methods

- The primary analysis was to calculate the relative efficacy of LAIV vs TIV by time interval (0–4 months and >4 mo postvaccination) against culture-confirmed influenza caused by antigenically similar strains for each of the 3 comparative studies.
- The relative efficacy and exact 95% CI were calculated using the same statistical methods as prespecified for the original study analysis.[2-4]
  - During each time interval, only a subject's first case of influenza during the study was counted.
- A secondary analysis was the relative efficacy of LAIV vs TIV by time interval against antigenically dissimilar strains.
- For Belshe et al, similarity for influenza B viruses was determined using genetic sequence analysis, as previously described,[17,18] given the heterogeneity of circulating B strains.

Results

- Across all studies, culture-confirmed influenza cases occurred 1.8–7.5 months postvaccination, and 51% of cases occurred in the 0- to 4-month interval **(Table 1)**.

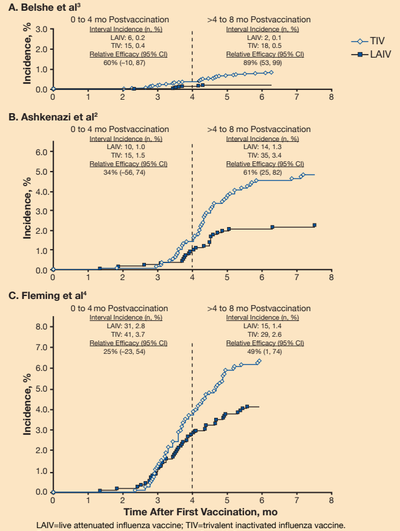
Table 1. Timing of Influenza Cases by Study

Study	Age at Enrollment	Influenza Season	Influenza Case Incidence, Months Postvaccination, Range	Matched Cases Occurring 0–4 mo Postvaccination, %
Belshe et al[3]	6–59 mo	2004–2005	2.0–7.1	51
Ashkenazi et al[2]	6–71 mo	2002–2003	1.8–7.5	33
Fleming et al[4]	6–17 y	2002–2003	2.4–5.9	62
Combined	NA	NA	1.8–7.5	51

NA=not applicable.

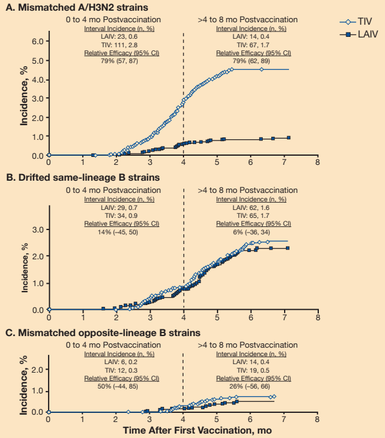
- In each study, LAIV recipients had less influenza than TIV recipients in the early and late time intervals, and the relative efficacy of LAIV compared with TIV increased from the 0- to 4-month interval to the 4- to 8-month interval **(Figure 1)**.
- For the Belshe[3] and Ashkenazi[2] studies, this relative efficacy trend was underscored by the disproportionate number of cases among TIV recipients compared with LAIV recipients in the final months of the influenza season.
  - In the Belshe study,[3] there were no LAIV cases of antigenically similar influenza after 5 months postvaccination, whereas there were 7 cases among TIV recipients; in the Ashkenazi study[2], there were 3 LAIV and 13 TIV cases after 5 months postvaccination.
- Analysis of results by individual strain **(Table 2)** revealed similar results for the predominant matched strain in each study: A/H1N1 in Belshe et al,[3] and influenza B in Ashkenazi et al[2] and Fleming et al.4 Efficacy against mismatched strains is presented in **Table 3**.
- A pooled analysis of all 3 studies indicated that there were 34% (95% CI: 3, 55) fewer cases among LAIV recipients at 0–4 months and 62% (95 CI: 42, 76) fewer cases among LAIV recipients at 4–8 months postvaccination.
- Only 1 study (Belshe et al[3]) had significant circulation of antigenetically dissimilar strains. In that study, the relative efficacy for mismatched strains was similar in both time intervals **(Figure 2)**.

Figure 1. Incidence of Culture-Confirmed Influenza Illness Caused by Antigenically Similar Strains



LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
Each symbol denotes a case of culture-confirmed influenza.

Figure 2. Incidence of Culture-Confirmed Influenza Illness Caused by Antigenically Dissimilar Strains (Belshe et al[3])



LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
Each symbol denotes a case of culture-confirmed influenza.

Conclusions

- **The relative efficacy of LAIV compared with TIV against antigenically similar strains of influenza increases over time.**
- **Because previous placebo-controlled studies have shown that the absolute efficacy of LAIV in children against matched strains has been comparable through 12 months postvaccination,[10,11] the current results suggest that the absolute efficacy of TIV in children is lower at 4–8 months postvaccination compared with 0–4 months.**
- **Multiple previous immunogenicity studies have shown that TIV-induced serum antibody levels decline in children by 4–9 months postvaccination.[12-15]**
  - **One study challenged TIV-vaccinated children at 12 months postvaccination with a cold-adapted influenza virus and demonstrated negligible residual immunity.[16]**
- **In the current analysis, the trend of increased relative efficacy of LAIV compared with TIV at 4–8 months postvaccination was not seen with antigenically dissimilar strains.**
  - **In placebo-controlled studies in children, LAIV has demonstrated high efficacy against mismatched influenza A strains,[19-21] whereas studies have concluded that TIV efficacy in children against mismatched influenza A is low.[21-24]**
  - **Therefore, the relative efficacy of LAIV compared with TIV against mismatched A/H3N2 in the Belshe[3] study would be expected to be high and similar over time.**
- **Further research is needed to explore these findings and to characterize the duration of protection provided by TIV against culture-confirmed influenza in children.**

Table 2. Relative Efficacy of LAIV vs TIV Against Matched Strains by Time Interval and Strain*

Study	Strain	Early (0–4 mo Postvaccination) LAIV, n (%)	Early (0–4 mo Postvaccination) TIV, n (%)	Early (0–4 mo Postvaccination) Relative Efficacy, % (95% CI)	Late (4–8 mo Postvaccination) LAIV, n (%)	Late (4–8 mo Postvaccination) TIV, n (%)	Late (4–8 mo Postvaccination) Relative Efficacy, % (95% CI)
Belshe et al[3]	**Any**	**6 (0.2)**	**15 (0.4)**	**60 (–10, 87)**	**2 (0.1)**	**18 (0.5)**	**89 (53, 99)**
	A/H1N1	**2 (0.1)**	**10 (0.3)**	**80 (6, 98)**	**1 (0.0)**	**17 (0.4)**	**94 (62, 100)**
	A/H3N2	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
	B	4 (0.1)	5 (0.1)	20 (–274, 84)	1 (0.0)	1 (0.0)	–1 (–7790, 99)
Ashkenazi et al[2]	**Any**	**10 (1.0)**	**15 (1.5)**	**34 (–56, 74)**	**14 (1.3)**	**35 (3.4)**	**61 (25, 80)**
	A/H1N1	0 (0.0)	0 (0.0)	NA	0 (0.0)	8 (0.8)	100 (42, 100)
	A/H3N2	3 (0.3)	2 (0.2)	–48 (–1670, 83)	9 (0.9)	4 (0.4)	–122 (–886, 38)
	B	**7 (0.7)**	**13 (1.3)**	**47 (–43, 82)**	**5 (0.5)**	**24 (2.3)**	**80 (45, 94)**
Fleming et al[4]	**Any**	**31 (2.8)**	**41 (3.7)**	**25 (–23, 54)**	**15 (1.4)**	**29 (2.6)**	**49 (1, 74)**
	A/H1N1	0 (0.0)	0 (0.0)	NA	0 (0.0)	5 (0.5)	100 (–8, 100)
	A/H3N2	4 (0.4)	7 (0.6)	43 (–123, 88)	8 (0.7)	5 (0.5)	–59 (–518, 54)
	B	**27 (2.4)**	**34 (3.1)**	**21 (–35, 54)**	**7 (0.6)**	**19 (1.7)**	**63 (9, 87)**

LAIV=live attenuated influenza vaccine; NA=not applicable; TIV=trivalent inactivated vaccine.
*Data for any strain and the predominant matched strain in each study is in bold.

Table 3. Relative Efficacy of LAIV vs TIV Against Mismatched Strains by Time Interval and Strain

Study	Mismatched Strain	Early (0–4 mo Postvaccination) LAIV, n (%)	Early (0–4 mo Postvaccination) TIV, n (%)	Early (0–4 mo Postvaccination) Relative Efficacy, % (95% CI)	Late (4–8 mo Postvaccination) LAIV, n (%)	Late (4–8 mo Postvaccination) TIV, n (%)	Late (4–8 mo Postvaccination) Relative Efficacy, % (95% CI)
Belshe et al[3]	A/H1N1	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
	A/H3N2	23 (0.6)	111 (2.8)	79 (67, 87)	14 (0.4)	67 (1.7)	79 (62, 89)
	Same-lineage B	29 (0.7)	34 (0.9)	14 (–45, 50)	62 (1.6)	66 (1.7)	6 (–36, 34)
	Opposite-lineage B	6 (0.2)	12 (0.3)	50 (–44, 85)	14 (0.4)	19 (0.5)	26 (–56, 66)
Ashkenazi et al[2]	A/H1N1	0 (0.0)	0 (0.00)	NA	0 (0.0)	2 (0.2)	100 (–425, 100)
	A/H3N2	2 (0.2)	2 (0.2)	1 (–1260, 93)	4 (0.4)	4 (0.4)	1 (–429, 82)
	B	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (0.1)	100 (–3744, 100)
Fleming et al[4]	A/H1N1	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (0.1)	100 (–3775, 100)
	A/H3N2	1 (0.1)	1 (0.1)	1 (–7700, 99)	4 (0.4)	0 (0.0)	NA*
	B	0 (0.0)	1 (0.1)	100 (–3775,100)	1 (0.1)	1 (0.1)	1 (–7700, 99)

References

1. Fiore AE, et al. *MMWR Recomm Rep.* 2009;58(RR-8):1-52.
2. Ashkenazi S, et al. *Pediatr Infect Dis J.* 2006;25(10):870-879.
3. Belshe RB, et al. *N Engl J Med.* 2007;356(7):685-696.
4. Fleming DM, et al. *Pediatr Infect Dis J.* 2006;25(10):860-869.
5. SDI. SDI Reports: Number of flu vaccines given in physicians' offices up 237% so far this year. Available at: http://www.sdihealth.com/about_us/releases/FLU_PR9_2_09.pdf. Accessed December 18, 2009.
6. Bhatt P, et al. Real-time assessment of 2008-2009 influenza vaccine utilization among practicing pediatricians [Abstract 753221]. Presented at: Pediatric Academic Societies' Annual Meeting; May 2-5, 2009; Baltimore, MD.
7. American Academy of Pediatrics. Recommendations for prevention and control of influenza in children, 2009-2010. Available at: http://aapredbook.aappublications.org/news/FluPolicy2009-10.pdf. Accessed December 3, 2009.
8. Centers for Disease Control and Prevention. Live, intranasal influenza vaccine: what you need to know, 2009-10. Available at: http://www.cdc.gov/vaccines/pubs/vis/default.htm#flu. Accessed December 3, 2009.
9. Centers for Disease Control and Prevention. Inactivated influenza vaccine: what you need to know, 2009-10. Available at: http://www.cdc.gov/vaccines/pubs/vis/default.htm#flu. Accessed December 3, 2009.
10. Ambrose CS, et al. *Pediatr Infect Dis J.* 2008;27(8):744-748.
11. Tam JS, et al. *Pediatr Infect Dis J.* 2007;26(7):619-628.
12. Wright PF, et al. *Pediatr Infect Dis J.* 2008;27(11):1004-1008.
13. Noble GR, et al. *Dev Biol Stand.* 1977;39:253-260.
14. Lerman SJ, et al. *J Pediatr.* 1980;96(2):271-274.
15. Johnson PR, Jr., et al. *J Med Virol.* 1985;17(4):325-335.
16. Johnson PR, et al. *J Infect Dis.* 1986;154(1):121-127.
17. Belshe RB, et al. Genetic sequences of circulating 2004–2005 influenza strains and serum antibody responses to LAIV vs TIV in young children. Presented at: Joint Meeting of the Pediatric Academic Societies and Asian Society for Pediatric Research; May 2-6, 2008; Honolulu, HI.
18. Belshe RB, et al. *Vaccine.* 2009:doi:10.1016/j.vaccine.2009.1011.1068.
19. Gaglani MJ, et al. *Arch Pediatr Adolesc Med.* 2004;158(1):65-73.
20. Belshe RB, et al. *J Pediatr.* 2000;136(2):168-175.
21. Piedra PA, et al. *Pediatrics.* 2007;120(3):e553-564.
22. Ritzwoller DP, et al. *Pediatrics.* 2005;116(1):153-159.
23. Belongia EA, et al. *J Infect Dis.* 2009;199(2):159-167.
24. Skowronski DM, et al. *J Infect Dis.* 2009;199(2):168-179.

Conflict of Interest: Drs. Ambrose and Wu are employees of MedImmune, LLC. Dr. Belshe has served as a consultant and/or member of a speakers bureau for MedImmune, GlaxoSmithKline, and Novartis.

44th National Immunization Conference; April 19–22, 2010; Atlanta, Georgia