Live Attenuated Influenza Vaccine: Will the Phoenix Rise Again?

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The live attenuated influenza vaccine (LAIV) (FluMist) has undergone a roller coaster journey since its licensure in 2003 for eligible individuals 5 to 49 years of age and subsequent expansion to children 2 to 4 years of age in 2007. LAIV was the first new influenza vaccine approved in the United States since the introduction of the inactivated influenza vaccine (IIV) developed in the 1940s. Authors of studies performed before the influenza A/H1N1 2009 pandemic (A/H1N1pdm09) suggested that LAIV was more efficacious than IIV in pediatric populations.[1] The Advisory Committee on Immunization Practices (ACIP) from the Centers for Disease Control and Prevention recommended preferential use of the LAIV for eligible children 2 to 8 years of age in the 2014–2015 season, removed the preferential recommendation in the 2015–2016 season, and provided interim recommendation against its use during the 2016–2017 and 2017–2018 seasons because of observational studies suggesting effectiveness that would be lower than expected against the A/H1N1pdm09.[2–5]

The study by Chung et al,[6] "Live Attenuated and Inactivated Influenza Vaccine Effectiveness" in this issue of *Pediatrics* is a meta-analysis from 5 observational programs conducted from 2013–2014 through 2015–2016 comparing vaccine effectiveness between live attenuated influenza vaccine–quadrivalent (LAIV4) and IIV among children 2 to 17 years of age. The studies were conducted in outpatient settings, and vaccine effectiveness was calculated from a test-negative case-control design comparing odds of vaccination among influenza-positive cases to influenza-negative controls. Overall, the 5 surveillance projects revealed reduced effectiveness against A/H1N1pdm09 for LAIV4 compared with IIV and was used to provide a compelling argument why ACIP made the interim recommendation against its use during the 2016–2017 and 2017–2018 seasons.

LAIV was originally developed by Hunein Maassab in the 1960s.[7] Two master strains were generated: (1) influenza A/Ann Arbor/6/60 (H2N2) used in the formulation of A/H1N1pdm09 and H3N2 vaccine strains and (2) influenza B/Ann Arbor/1/66 used in the production of influenza B Yamagata and B Victoria vaccine strains.[7,8] LAIV has the cold-adapted, temperature-sensitive, and attenuated phenotype of the master donor viruses and is updated annually with genes from contemporary viruses. LAIV's mechanism of action involves viral replication in the ciliated epithelial cells of the nasopharyngeal mucosa inducing immune responses that mimic those of natural influenza viral infection including mucosal immunoglobin A antibody production and strong cell-mediated immunity.[9,10] It was found in a meta-analysis of 14 randomized controlled trials, 8 cohort studies, 1 case-control study, and 1 randomized controlled trial that live attenuated influenza vaccine–trivalent (LAIV3) had 79% efficacy in children >2 years of age compared with a placebo or no immunization.[1] LAIV3 has been shown to protect against seasonal influenza A/H1N1, including new variants (before the replacement by A/H1N1pdm09), and

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to reduce influenza-related morbidity at the community level through herd protection.[11]

This begs the question, "Why did LAIV4 vaccine effectiveness performance decline, and can it recapture its past performance when it was a trivalent formulation?" Potential causes were reviewed at the 2016 World Health Organization meeting on LAIV effectiveness.[12] Discussed were methodological study differences; inadequate vaccine handling at vaccine distribution centers; intrinsic virological characteristics of the novel A/H1N1pdm09, in particular, the influenza A/California/7/2009 strain used in the initial formulations of LAIV4; and increased preexisting population immunity in the United States because of improved influenza vaccine coverage among all ages since the 2010 ACIP universal influenza vaccine recommendation. Another consideration is viral interference with the addition of a second influenza B strain that occurred when the vaccine composition changed from LAIV3 to LAIV4 for the 2013–2014 season. Complicating the data from the United States were the results from other countries indicating reasonable level of protection against the A/H1N1pdm09 and protection against influenza A/H3N2 and influenza B similar to or better than IIV, consistent with the findings reported by Chung et al[6] for influenza B.

ACIP has now again recommended the use of LAIV4 as an option for vaccine providers for the 2018–2019 season.[13] This was based, in part, on manufacturer data revealing improved viral shedding and immunogenicity in children 2 to 4 years of age. LAIV4 contained an updated A/H1N1pdm09 vaccine strain, influenza A/Slovenia/2903/2015, with improved viral growth properties. Estimates on vaccine effectiveness were not available at the time of ACIP recommendation.

Recently, an interim analysis on vaccine effectiveness for the 2017–2018 season has emerged from Public Health England.[14] The United Kingdom began introducing a universal influenza vaccine program for children in the 2012–2013 season primarily using LAIV. Annual estimates of influenza vaccine effectiveness are also determined by using a test-negative case-control design. The interim end-of-season adjusted vaccine effectiveness for LAIV4 in children and adolescents 2 to 17 years of age was 90.3% (95% confidence interval: 16.4%–98.9%) against A/H1N1pdm09 for the 2017–2018 season. The LAIV4 formulation contained influenza A/Slovenia/2903/2015 (A/H1N1pdm09) that is also present in the 2018–2019 LAIV4 formulation. This early result is encouraging and supports the reintroduction of LAIV4 in the United States as an option for the control of seasonal influenza. It also highlights the need for annual influenza vaccine effectiveness estimates and the importance of the US Influenza Vaccine Effectiveness Network in providing updated information for ACIP recommendations.

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
A/H1N1pdm09: influenza A/H1N1 2009 pandemic
IIV: inactivated influenza vaccine
LAIV: live attenuated influenza vaccine
LAIV3: live attenuated influenza vaccine–trivalent
LAIV4: live attenuated influenza vaccine–quadrivalent

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