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Live Attenuated Influenza Vaccine in Children

Christopher S. Ambrose, MD, Robert E. Walker, MD, and Edward M. Connor, MD

Live attenuated influenza vaccine (LAIV) offers a novel approach to influenza vaccination and is approved for healthy individuals 5 to 49 years of age. In placebo-controlled studies in children, LAIV was 73 to 93 percent efficacious, and protection lasted more than 12 months. In head-to-head studies in children, LAIV demonstrated a 35 to 53 percent reduction in influenza attack rates compared with injectable influenza vaccine (TIV) for matched strains. Compared with TIV, LAIV has demonstrated broader serum antibody responses, particularly against mismatched influenza A. The most common adverse events are runny nose and nasal congestion. Increased rates of asthma events were observed in young children. Additional large-scale safety and efficacy studies in young children, including a formal risk-benefit assessment, are ongoing. The results of these analyses will guide potential future use in young children.
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Despite increasing vaccination rates among high-risk populations, influenza continues to cause significant morbidity and mortality on an annual basis, resulting in approximately 25 million physician visits and 36,000 deaths per year in the United States.[1-3] Although influenza illness occurs in all age groups, attack rates are highest in children,[3-6] and there is growing appreciation that young children are at increased risk of hospitalization and serious illness as the result of influenza.[7-9] Children also are considered the primary vectors of influenza in the community,[3,6] and high levels of pediatric vaccination have been shown to reduce the overall burden of disease at the community and societal levels, including reductions in the rates of mortality in elderly populations.[3,10,11] Influenza vaccination now is universally recommended in children 6 months to 5 years of age in the United States in an effort to decrease their high rates of hospitalization and disease.[12]

Live attenuated influenza vaccine (LAIV, FluMist®) offers a novel approach to influenza vaccination. The protection provided by LAIV has been described in multiple clinical studies in children of various ages. Although the vaccine currently is approved for use in healthy children and adults 5 to 49 years of age, the U.S. Food and Drug Administration (FDA) is evaluating studies that were conducted to provide support for approval in younger children.

MedImmune, Inc., Gaithersburg, MD.
Address reprint requests to Christopher Ambrose, MD, Senior Associate, Clinical Development, MedImmune, Inc., One MedImmune Way, Gaithersburg, MD 20878.

Background

LAIV is a live, attenuated, trivalent influenza vaccine for intranasal administration. Each dose of vaccine contains 10^7 viral particles of 1 type B and 2 type A (ie, A/H1N1 and A/H3N2) attenuated, cold-adapted reassortant influenza virus strains. The reassortant vaccine strains, updated annually to match the target strains selected by the U.S. Public Health Service, are produced through cocultivation of targeted wild-type strains with cold-adapted, attenuated master donor viruses. The resulting three vaccine strains retain the cold-adapted, temperature-sensitive, attenuated properties of the master donor viruses but express the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins of the targeted wild-type strains (Fig. 1). In the future, reverse genetics technology will be used to construct new vaccine strains. Use of reverse genetics (also known as "plasmid rescue") technology enhances the safety, specificity, reliability, and efficiency with which new vaccine strains can be produced.

Two formulations of LAIV have been developed for commercial use. The currently licensed formulation of LAIV (FluMist®) requires storage at −15°C or less and is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy individuals 5 to 49 years of age. CAIV-T, derived from the same attenuated, cold-adapted master donor viruses used to manufacture frozen FluMist, is an investigational formulation that is stable at refrigerator temperatures of 2°C to 8°C. The two formulations are designed to have comparable potency per dose. Comparable immunogenicity and safety in healthy children and adults 5 to 49 years of age have been reported.[13]

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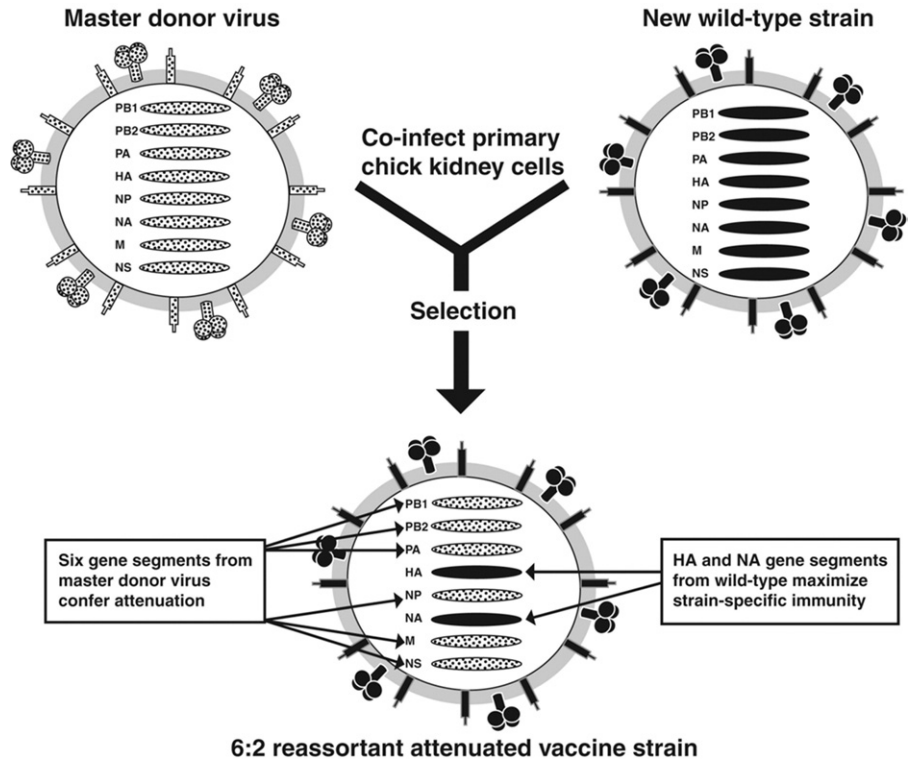

Figure 1 Co-cultivation of targeted wild-type strains with cold-adapted, temperature-sensitive, attenuated master donor viruses produces LAIV vaccine strains that closely resemble the targeted wild-type influenza strains but retain the attenuated characteristics of the master donor virus and, hence, do not cause influenza disease. Master donor viruses for both A and B strains are used to generate the updated vaccine strains each year.

Immune Response to Influenza

Natural immunity to wild-type influenza results primarily from both serum (primarily IgG) and mucosal (primarily secretory IgA) antibodies. Anti-HA and -NA antibodies have been correlated with resistance to influenza illness; anti-HA antibodies neutralize the virus and prevent cellular infection, whereas anti-NA antibodies block viral release from infected cells.[14-16] Although serum antibodies primarily are responsible for lower respiratory tract protection and are the most commonly measured correlate of protection from illness, local mucosal antibodies are critical for protection of the upper respiratory tract and may be more important to overall protection against infection.[16-20] In addition to antibody-mediated immunity, cytotoxic T-cell responses directed against conserved core proteins (such as the matrix [M] and nucleoprotein [NP]) play a significant role in recovery from illness and viral clearance and a minor role in protection against illness.[15,16,21-23] Innate immune responses, such as the production of interferon, also appear to contribute to protection from influenza, particularly during the early stages of infection.[14,24]

As a result of accumulated mutations in the influenza genome, antigenic variants of circulating wild-type influenza strains continually emerge. These drifted, variant strains can evade some of the preexisting immunity in the population.[14,15] Secretory IgA antibodies and, to a lesser extent, cytotoxic T-cells and serum IgG antibodies have demonstrated cross-reactivity between antigenically distinct influenza strains within the same subtype.[14,18,22,25] These cross-reactive immune mechanisms become particularly relevant when a novel, drifted strain emerges in the community.

The Rationale for LAIV

As a live, attenuated, mucosally administered vaccine, LAIV is designed to induce an immune response that resembles the response generated by infection with wild-type influenza without causing influenza disease. Conventional intramuscular injection of trivalent inactivated influenza vaccine (TIV) primarily stimulates a serum antibody response against the HA proteins, with the greatest response being seen in already-primed individuals who have had previous immunologic exposure to influenza.[15,16,26] LAIV vaccine strains are administered intranasally and replicate in the respiratory epithelium of the nasal mucosa to induce influenza virus-specific serum and mucosal antibodies, cytotoxic T-cell responses, and interferon.[15,16] As a live, attenuated vaccine, LAIV has the potential to induce broad and durable protection against influenza. This expectation, along with the advantage of convenient, needleless administration, was the primary impetus for the clinical development of LAIV.

Efficacy in Placebo-Controlled Studies

LAIV consistently has demonstrated high levels of protective efficacy against antigenically matched influenza strains in