Live, Attenuated Influenza Vaccine: Is Past Performance a Guarantee of Future Results?

Ravi Jhaveri, MD

Division of Infectious Diseases, Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, North Carolina

ABSTRACT

Purpose: Live, attenuated influenza vaccine (LAIV) has had a tumultuous recent history that can be difficult for many to follow and understand. This commentary reviews the origin of LAIV; the events and circumstances that led to the withdrawal of any recommendation pf LAIV use in the United States; the merits, shortcomings, and repercussions of that decision; and finally some thoughts about the future of LAIV.

Methods: [List of databases, eg, PubMed] were searched for relevant articles. The reference lists of identified articles were searched manually for additional papers eligible for inclusion.

Findings: Prior to 2013, LAIV had a record of accomplishment of providing equal or greater protection against influenza in children. Since 2013, concerns about the lack of protection with LAIV against pandemic H1N1 strains led to the withdrawal of any recommendation of its use in the United States by the Advisory Committee on Immunization Practices. After some significant changes to the content, evaluation, and production of LAIV, it has been recommended again for use in the United States in the 2018–2019 influenza season.

Implications: One can debate the merits of whether LAIV should have been removed from use, but it is likely that many years from now, the recent "ups and downs" of LAIV will only be an interesting footnote in history. (*Clin Ther*. 2018;■:1–9) © 2018 Elsevier Inc. All rights reserved.

Key words: influenza, live attenuated vaccine, recommendations, United States.

INTRODUCTION

The 2017–2018 influenza (flu) season was the most active since the pandemic 2009 season and marked the second season in a row that the Advisory Committee for Immunization Practices (ACIP) did not recommend the live, attenuated influenza vaccine (LAIV) for use in preventing flu in the United States. LAIV has had a tumultuous recent history, with many changes in its status: it was approved for many years, then it was preferred, then it was not preferred, then it was not even recommended, and next season it will return as an option but without a preference. All of these changes have happened in the past 5 years and are difficult to understand without a significant amount of explanation. The goals of this commentary are to explain this complicated history and to offer some perspective on what the future may hold for LAIV and flu prevention.

MATERIALS AND METHODS

[List of databases, eg, PubMed] were searched for English-language [article/study types] articles published between xxx and xxx [range publication years searched], using the key terms [list of key terms in italics]. The reference lists of identified articles were searched manually for additional papers eligible for inclusion. Data from articles that were [article/study types excluded] were excluded from the commentary.

RESULTS

A total of [number] articles were identified from the database searches. After the exclusion of [number]

Accepted for publication July 2, 2018.
https://doi.org/10.1016/j.clinthera.2018.07.003
0149-2918/$ - see front matter

articles that were [reasons for exclusion], data from [number] articles (N = [total number of patients]) were included in the present commentary.

Brief Review of Flu Basics

The reader is referred elsewhere for a detailed explanation of flu proteins, biology, and life cycle.[1] In any given season, one *A strain* will dominate, with *B strains* causing varying amounts of infection that peak toward the end of the season. It is very difficult to predict which strain will dominate in any given season. Seasonal vaccine strains are selected for inclusion in February to allow time for preparation of vaccine for September delivery. Interim estimates of flu vaccine efficacy usually become available between February and June, but final figures are usually not available until September or October, just prior to the following season.

LAIV History: Pre-2013

There had long been an interest in developing an intranasal LAIV. The intramuscular version of the vaccine, termed *injectable influenza vaccine* (IIV), had been used for decades and offered consistent, modest protection against flu infection. However, advocates for a live, intranasal version argued that local replication and stimulation of immunity in the upper airway would offer distinct advantages in protecting against respiratory infection.

In the mid-1960s, Maassab[2] began to work on cold adaptation of influenza virus using serial passage of viral isolates in primary chick kidney cultures. He demonstrated that viral growth at 25°C could occur to high levels and that growth at physiologic temperatures was reduced compared to that of wild-type parent strains. Over the next 25 years, attenuated A/H1, A/H3 and B isolates were meticulously studied in adults and children to demonstrate that they were well tolerated, immunogenic, and efficacious separately and when combined into a trivalent vaccine candidate.[3–5] In 1995, Aviron (now MedImmune Vaccines, Gaithersburg, Maryland) acquired the rights to develop the LAIV, in cooperation with the National Institute for Allergy and Infectious Diseases and via a licensing agreement with the University of Michigan.[6] In a large, double-blind, placebo-controlled study in >3000 children during the 1997–1998 season, LAIV demonstrated >90% protection against influenza infection.[7] Aviron applied for licensure from the US Food and Drug Administration in 2000, and in 2003 LAIV was approved for use in children and adults aged 5 to 49 years. In anticipation of product approval, MedImmune acquired Aviron and the rights to LAIV in December 2001.[8] Other subsequent modifications to the preparation and labeling of LAIV included a switch from a frozen to a liquid formulation in 2007 and an expanded age limit down to 2 years of age.[9] In April 2007, the British pharmaceutical company AstraZeneca bought MedImmune.[10] In February 2012, MedImmune received approval from the Food and Drug Administration to change the formulation of LAIV from trivalent (one H1 strain, one H3 strain, and one B strain) to quadrivalent (inclusion of an additional B strain).[9]

After initial approval, LAIV saw a slow but steady increase in the number of annual doses distributed, from 2,036,560 doses in 2004–2005 to a peak in 2014–2015 of 13,905,040 quadrivalent doses (personal communication, A. Bandell, MedImmune). There was significant interest in whether LAIV was more efficacious compared with IIV, and several studies sought to answer this question in both children and adults. Fleming et al[11] studied LAIV versus IIV in a cohort of children with a known diagnosis of asthma and demonstrated that LAIV had a 35% greater relative efficacy than IIV in preventing flu. Ashkenazi et al[12] studied LAIV versus IIV in a cohort of children with recurrent respiratory infection and demonstrated fewer cases of confirmed influenza in the LAIV group. The largest-scale study was performed in >8000 children across the United States and Europe in the 2004–2005 season.[13] That study showed >50% fewer cases of influenza among LAIV recipients compared to those who received IIV. Notable among the results was that protection with LAIV was significant even against H3N2 strains that were considered a poor match for vaccine strains. Despite the significantly greater LAIV efficacy observed in children, comparable studies in adults showed opposite results[14]: While LAIV did offer some protection in adults, IIV offered a greater degree of protection.

Based on the increased efficacy observed in the pediatric studies, several countries began issuing preferential recommendations for using LAIV in children. In 2011, the National Advisory Committee on Immunization in Canada expressed a preference for the use of LAIV in children aged 2 to 17 years that continued though the 2013–2014 season.[15–17] In July 2012, the Joint