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

Live attenuated influenza vaccine (LAIV) has had a tumultuous recent history that can be difficult for many to follow and understand. Prior to 2013, LAIV had a record of accomplishment of providing equal or superior 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 for use in the US by the Advisory Committee on Immunization Practices (ACIP). After some significant changes to the content, evaluation and production of LAIV, it has been be recommended again for use in the US in 2018-19. This commentary reviews the origin of LAIV, the events and circumstances that led to the withdrawal of any recommendation for LAIV use by the ACIP, the merits, shortcomings and repercussions of that decision and finally offers some thoughts about the future of LAIV. (*Clin Ther*. 2018;40:1246–1254)

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.

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

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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 Committee on Vaccination and Immunisation in the United Kingdom issued a statement recommending the school-based expansion of flu vaccination in low-risk children, and the preferential use of LAIV due to its greater efficacy and convenient administration.[18] For the 2013–2014 season, the Standing Committee on Immunization in Germany recommended that LAIV be used in children aged 2 to 6 years in preference to IIV.[19]

The Table offers a summary of individual flu seasons, flu vaccine efficacy, a timeline of ACIP decisions, and other relevant events.

LAIV in the 2014–2015 Season

For the 2014–2015 season, the US ACIP decided to issue a preferential recommendation to use LAIV over IIV in children aged 2 to 8 years.[20] The decision was announced after the June 2014 meeting and published in September 2014, prior to the final vaccine efficacy results from the 2013–2014 season. One month later, at the regularly scheduled October 2014 meeting, final LAIV efficacy data were presented for the prior 2013–2014 season.[23] The results showed no demonstrable protection against the prevailing H1N1 strain in that season, while there was continued H1N1 efficacy of IIV. The Centers for Disease Control and Prevention (CDC) and ACIP issued a statement that, since the upcoming 2014–2015 season appeared to be one in which the H3N2 strain would be likely to predominate, there was no need for any change in the recommendations for that season.[24] With the timing so soon after the ACIP issued a preferential recommendation of LAIV use in children, this news likely had a tremendous adverse impact on the public's perception and on the ACIP itself.

An initial analysis by MedImmune into the lack of H1N1 efficacy in 2013–2014 yielded some very

interesting insights. The H1N1 component of the 2013–2014 vaccine was A/California/7/2009, which has a substitution of glutamine to lysine in the stalk of the hemagglutinin protein. This substitution renders the protein much more susceptible to degradation at higher temperatures.[25] MedImmune and other researchers determined that the LAIV efficacy in 2013–2014 was very dependent on geography.[26] LAIV used in colder regions of the United States and Canada demonstrated vaccine efficacy in the typical range of 50% to 60%, while LAIV shipped to warmer regions of the United States had no demonstrable protection. The analysis showed that shipping and handling practices resulted in significant exposure of LAIV lots to high temperatures in the late summer months.[27] The prevailing hypothesis was that heat exposure led to degradation of this heat-labile H1N1 strain and thus lowered the efficacy of the LAIV in that season. In response, MedImmune replaced the H1N1 strain, modified shipping protocols, and assumed that they had corrected the problem. It is important to also note that the 2013–2014 season, with reduced H1N1 efficacy, was the first in which MedImmune manufactured LAIV as a quadrivalent vaccine.[9]

As it turns out, in 2014–2015 a "drifted" H3N2/Switzerland strain emerged that was not a good match for the H3N2 isolate in any vaccine. As a result, flu vaccine efficacy was very poor for all vaccine preparations.[28]

LAIV in 2015–2016, the ACIP Meeting June 2016: a Pattern Emerges With Total Withdrawal

ACIP recommendations for 2015–2016 removed any preference for LAIV and included LAIV and IIV as equal options for the prevention of flu.[29] The prevailing strain that circulated in 2015–2016 was the 2009 H1N1 strain, and the interim estimates of vaccine efficacy at the end of the season again showed reduced efficacy of LAIV compared to IIV.[30,31]

The ACIP discussed these results at the June 2016 meeting. Data derived from the CDC-sponsored, multicenter national network demonstrated near-zero efficacy of LAIV while IIV offered about 60% protection.[32] Data derived from smaller samples from the US Department of Defense surveillance program, from MedImmune's own surveillance network, and from international sources all demonstrated lesser efficacy of LAIV against the H1N1 circulating strain, but estimates ranged from a low of 15% to a high of 58%.[32–35] Because the LAIV lots for 2015–2016 included a 2009 H1N1 strain that was more heat stable, and because MedImmune corrected its shipping and delivery protocols, clearly other factors contributed to the lesser LAIV efficacy against the H1N1 strain. The most significant change that had taken place in the years of lesser efficacy of LAIV was the switch from a trivalent to a quadrivalent formulation. While there were no specific concerns in any of the studies about LAIV protection against H3N2 strains or B strains, the lack of efficacy of quadrivalent LAIV against the H1N1 strain in the CDC-sponsored surveillance study was striking.[32]

A special working group met and drafted recommendations for the ACIP to consider.[32] The first option was that LAIV should not be used in any circumstances due to the reduced efficacy against H1N1. This option reflected the public health concern that a quadrivalent vaccine with poor efficacy against one strain would still be considered ineffective despite efficacy against the other strains, and therefore should not be recommended. The second option was that LAIV should be limited due to concerns about reduced efficacy against H1N1 and because IIV raised none of those concerns. In this 2nd option, LAIV would be used only when IIV was refused, if there was a shortage of IIV, or if a school-based program was using LAIV with no alternative option. The members of the ACIP considered the options and the merits and limitations of both positions. After much deliberation, a general consensus was formed around the idea that, given the concerns about LAIV efficacy and the lack of concerns about IIV, LAIV should not be recommended.[32] Public messages were issued to assist providers in preparing for the upcoming season and to communicate that this was an "interim" recommendation and could be reversed for future seasons based on new data.[36,37]

On review of the ACIP meeting transcript, there are other factors that do not appear to have been discussed and that would have supported the option for limited recommendation of LAIV use.[32] Given that 2 of the prior 3 seasons were dominated by pandemic H1N1 strains, it was very likely that the upcoming year was going to be an H3N2 season. While there was considerable uncertainty regarding the declined efficacy of LAIV against H1N1, none of the studies suggested that there should be concern about efficacy against H3N2 or against either B strain. As mentioned previously, data from the Department of Defense, MedImmune, and international sites all suggested that LAIV still offered

protection when compared to no vaccine. Older studies showed that one of the other benefits offered by LAIV compared to IIV was effective protection when H3N2 strains were less well matched with selected vaccine isolates.[12,13] By choosing the more limited recommendation for use of LAIV rather than recommending against its use, the ACIP could have allowed for additional time for the manufacturer to resolve the problem. This option came with the possible risk for having another H1N1 year with a vaccine with lesser efficacy, while the choice to solely recommend IIV eliminated this particular risk. While there was some mention of the use of LAIV in school-based programs, there was not significant discussion about the parental preference for intranasal administration of LAIV as opposed to an injectable vaccine. It has been previously noted that up to 10% of parents who received LAIV would have otherwise chosen no vaccine.[38] The lack of LAIV as an option may lead to reduced levels of vaccination. Given the potential for pandemic flu to emerge at any moment, a live, intranasal flu vaccine would be an important tool to combat a pandemic. After the emergence of the pandemic H1N1 strain in the spring of 2009, the following season LAIV was available well before IIV. Finally, there were the market ramifications of the withdrawal of the recommendation of LAIV. Without any ACIP recommendation for use, MedImmune's parent company, AstraZeneca, could have decided to stop producing LAIV. Because of the global market for LAIV, this halt in production did not happen. Perhaps these factors were discussed in some detail in private ACIP influenza working group discussions, but they are not represented in the transcript of the meeting.[32]

The timing of events must have been a huge factor in the ACIP decision-making process, from the ACIP issuing the preferential LAIV recommendation in June 2014, to the ACIP being confronted with poor efficacy data in October 2014, and ultimately to reversing the preferential recommendation in June 2015 only to be confronted with poor efficacy data again for 2015–2016. Perhaps without the seeming "back and forth" of the prior years, the ACIP would have opted for the limited recommendation of LAIV use instead of the total withdrawal of any recommendation of LAIV use.

Aftermath of June 2016: Fixing the Problem and Weighing the Repercussions

After the ACIP withdrew the recommendation of LAIV use, MedImmune conducted another intensive investigation to determine the nature of the problem with the pandemic H1N1 strain. A study of the replicative fitness of the H1N1 strains used in the quadrivalent LAIV from 2013 to 2016 showed significantly reduced viral replication of both the California and Bolivia strains.[21] Those studies also demonstrated poor binding to the α2,6-linked sialic acid residues in human alveolar cell lines and nasal epithelial cell cultures that are required for viral entry into cells.[39] These isolates had been previously cultivated in MDCK (dog kidney) cell lines, which is not a natural cell target for flu, as well as in unfertilized chicken eggs. The overall lower levels of H1N1 in the vaccine likely led to lower viral replication in the nasal epithelium of vaccine recipients, resulting in lesser efficacy. These results led to a change of the pandemic H1N1 strain included in LAIV in the future, with specific attention to replication in nasal epithelial cell cultures as a more relevant model for testing candidate flu strains.

It is important to consider the repercussions of the ACIP's decision and to evaluate the ways in which some of the aforementioned factors affected flu severity over subsequent seasons. During the 2016–2017 and 2017–2018 flu seasons, H3N2 did in fact dominate strain circulation, with very little H1N1 activity, so LAIV would likely have been an effective option. Final analysis of data from 2016–2017 showed that IIV efficacy against any flu strain in children aged 2 to 17 years was between 35% and 61%.[22] 2017–2018 was the most severe season of the past decade.[40] Review of interim estimates of flu vaccine efficacy from 2017–2018 demonstrated that IIV offered 36% efficacy in the US population overall, but only 25% against the predominant H3N2 strain, and showed essentially no detectable protection (−8%) in children aged 9 to 17 years.[41]

When considering parental preferences for the intranasal administration of LAIV, in 2016–2017 in the United States there was a 2% drop in the rate of flu vaccination among children aged 5 to 12 years and a 0.6% drop in the rate of flu vaccination in children aged 2 to 4 years.[42] The decline in flu vaccination rate in the group aged 5 to 12 years was the first drop after 5 straight years of increases. While 2% seems like a small figure, it represents 640,000 children who did not receive flu vaccine in 2016–2017 but who did in prior years. While it is impossible to know whether this decline in vaccine coverage is entirely due to the lack of LAIV as an option, other studies also demonstrated lower rates of flu vaccination among children in

2016–2017 with no LAIV recommendation.[43] The final 2017–2018 flu vaccination rates among US children are not yet available for the evaluation of whether this decline was sustained.

In a very basic attempt to quantify the impact of not having LAIV as an option during the 2017–2018 season, one can collate several different data sources to make an estimate. The most comparable recent season would be 2012–2013. While it was not quite as severe, H3N2 was the predominant strain, there were a comparable number of pediatric deaths (111) by the end of March, and the pneumonia and influenza–related mortality rate reached a similar point above the CDC's "epidemic threshold." The CDC has published 2 analyses based on data from 2012–2013 and other seasons that quantified the hospitalizations averted and illnesses prevented nationwide with flu vaccination across all ages.[44,45] In the 2012–2013 season, with 48.5% vaccine coverage and 46% efficacy in children aged 5 to 19 years, there were an estimated 4770 averted hospitalizations, almost 900,000 averted cases requiring medical attention, and >1.7 million total cases averted.[44] Using current interim estimates of the 2017–2018 season in this same age group, vaccine efficacy is likely to be ~25%, and vaccine coverage, ~60%. Assuming that the slight reductions in vaccine coverage were in fact due to the lack of LAIV and assuming that LAIV offered equal protection against the primary H3N2 strain, it is possible in this age group alone that having LAIV as an option in 2017–2018 could have averted 25,000 cases of flu and 10,000 cases that required medical attention.[44,45] If vaccine coverage was even lower this year among children aged 5 to 12 years and LAIV offered better protection against the H3N2 strain like in the United Kingdom last year, those estimates of potential cases averted could be much higher.

Despite the ACIP's decision and the lack of a US recommendation over the last 2 seasons, international use of LAIV with the same H1N1 strain was uninterrupted. In Canada, LAIV was still recommended for use in the 2016–2017 and 2017–2018 seasons, but the preferential recommendation for use in children was removed.[46] In Finland, estimates of LAIV efficacy in 2016–2017 in the nationwide immunization program were ~37%.[47] The United Kingdom continued to use LAIV for the school-based programs mentioned previously, with very effective results.[48,49] Across the United Kingdom during the 2016–2017 season, when the same H3N2 strain as in the United States was predominant, with little H1N1, LAIV efficacy in children aged 2 to 17 years was 65.8%.[48] The estimates against the H3N2 and B strains were 57% and 78.6% respectively. These results benefit from the clarity of hindsight, but support the notion that LAIV would likely have been an effective option for use in the United States.

February 2018 ACIP Meeting: Seeing the Path Ahead

The February 2018 ACIP meeting contained several key presentations. The interim estimates of IIV efficacy from the CDC network were presented, demonstrating very modest protection overall and no detectable protection in children aged 9 to 17 years.[41] The subsequent presentation was from Mallory, an investigator from MedImmune/AstraZeneca, discussing the results of LAIV efficacy using a new H1N1 Slovenia strain that demonstrated high-level replication in nasal epithelial cultures.[50] There were 200 children assigned to 1 of 3 equal groups, each given a different formulation of LAIV: 2015–2016 LAIV3, with the old H1N1 Bolivia strain; 2015–2016 LAIV4, with the old H1N1 Bolivia strain; and 2017–2018 LAIV4, with the new H1N1 Slovenia strain. Results with the new formulation showed that the 2017–2018 LAIV4 resulted in increased shedding of the H1N1 strain from the nose (a marker of increased replication in vivo) and higher serum antibody levels in vaccine recipients. While serum antibody levels have never been a primary end point for LAIV efficacy, Mallory pointed out that prior versions of LAIV with a 1999/New Caledonia H1N1 strain with high efficacy (80%–90%) also produced similar levels of serum antibody. After the presentation, CDC representatives reviewed all of the available data on LAIV efficacy and then summarized the working group discussions about how to revise the recommendations to potentially use LAIV in the United States in 2018–2019.[51] After these discussions, the ACIP decided to reinstate a recommendation of the use of LAIV in the 2018–2019 season. The recommendation reads, "For the 2018–2019 influenza season, immunization providers are recommended to administer any licensed, age-appropriate influenza vaccine (IIV, RIV, or LAIV). LAIV4 is an option for influenza vaccination for persons for whom it is otherwise appropriate."[52]

It should be noted that the American Academy of Pediatrics' Committee on Infectious Diseases (COID) subsequently chose to diverge from ACIP in its 2018–2019 recommendation of the use of LAIV.[53] In light of the prior

seasons of poor performance and the lack of experience with the new version of LAIV in a season when H1N1 was circulating, COID chose a limited recommendation of LAIV. COID expressed a clear preference for IIV and limited LAIV to use in those children who were eligible but would not otherwise receive vaccine.[53]

The Future With LAIV: Is Past Performance a Guarantee of Future Results?

It is difficult to know exactly what to expect in 2018–2019 with the return of LAIV as an option, largely because there are so many variables that come with every flu season: What strain will circulate?; How antigenically drifted will it be from the selected vaccine strains?; What will vaccine supply be and when will it be available?; Is there an entirely new strain that emerges to evade vaccine-induced protection? These questions are impossible to answer, but perhaps it is helpful to work through what is most likely.

Given that there have been 2 consecutive seasons with H3N2 predominating, 2018–2019 is likely to be an H1N1-dominant year. Review of the World Health Organization's flu circulation data from the Southern Hemisphere in April 2018, prior to the onset of their flu season, indicates that the few isolates present appeared to have been mostly H1N1.[54] While this finding is by no means a guarantee that H1N1 will predominate in the Northern Hemisphere later this year, it is a first indication. If H1N1 predominates, the good news is that the reformulated LAIV can perform in clinical practice in the United States, and both vaccine effectiveness and vaccine coverage can be evaluated. The temporary ineffectiveness of LAIV against H1N1 should be corrected with a new strain and improved methods of evaluating viral replication, and the clinical study data suggest that this is the case. The performance of LAIV against the H3N2 strain on an international level echoes the older studies that demonstrated equal if not greater protection compared to IIV.

It is very likely that the levels of LAIV distribution will quickly return to the prior levels and that patients and physicians will welcome the option of an intranasal vaccine, but the divergence of the AAP COID recommendation from that of the ACIP could have a dampening effect. While it is unlikely that the ACIP will offer a preferential recommendation of LAIV use at any point in the near future, other countries may do so sooner, if not next season. To be convinced, ACIP members would probably need to see CDC surveillance data from multiple years demonstrating more protection with LAIV compared to IIV or from new large-scale, randomized, controlled trials. These scenarios are not likely to happen.

In the search for lessons learned from these events, there are a few to consider. The inconsistency of LAIV efficacy data between the CDC network and other US and international sources should prompt a plan to guide future action. Perhaps a more Bayesian approach that de-emphasizes results that are dramatic outliers from prior observations would have helped the ACIP to opt for the more limited recommendation of LAIV use. While concerns about lesser efficacy against H1N1 was the primary reason for the ACIP's decision, other factors such as efficacy against all strains, patient preferences, vaccine coverage, erection of new barriers to flu vaccination by the restriction of options, and market forces should have played a role in the decision-making process. This consideration of other factors runs counter to the prevailing public health approach that a lack of efficacy against one strain in a multivalent vaccine nullifies the efficacy against other strains in the consideration of its recommendation for use. One positive aspect of these events is that MedImmune has now developed a better process for selecting and monitoring strains for inclusion in future versions of LAIV. As opposed to animal-derived immortalized cell lines, the process will now screen candidate flu vaccine strains for replication in cultured human nasal epithelial cells.[50] This model should be much more relevant to predicting how these strains will replicate in a vaccine recipient's nasal epithelium to produce the desired protective immunity. In the event that we do encounter a new pandemic flu strain in the near future, these processes will yield a more effective vaccine more quickly.

CONCLUSIONS

LAIV has been reinstated for use in 2018–2019. One can debate the merits of whether it 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.

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Address correspondence to: Ravi Jhaveri, MD, Division of Infectious Diseases, Department of Pediatrics, University of North Carolina School of Medicine, CB 7231, 101 Manning Drive, Chapel Hill, NC 27599-7231. E-mail: ravi.jhaveri@unc.edu