

Live attenuated influenza vaccine (LAIV): recent effectiveness results from the USA and implications for LAIV programmes elsewhere

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ABSTRACT

The USA has a long-standing paediatric influenza vaccination programme, including use of live attenuated influenza vaccine (LAIV). Following US evidence of apparent lack of vaccine effectiveness (VE) of LAIV in 2015/2016, particularly against A(H1N1)pdm09, the USA suspended the use of LAIV in the 2016/2017 season. The UK introduced LAIV for children in 2013/2014 and Finland in 2015/2016. Both countries have since been closely monitoring programme performance. In 2015/2016, the UK and Finland, unlike the USA, found evidence of significant VE of LAIV against laboratory-confirmed influenza. Several studies, however, reported relatively lower VE of LAIV against A(H1N1)pdm09 infection compared with inactivated influenza vaccine, although not for A(H3N2) or B. The reasons for these apparent differences remain under investigation. Both the UK and Finland continue to recommend the use of LAIV in children for the 2017/2018 season and are intensifying further monitoring of their childhood programmes against a range of end-points.

INTRODUCTION

Live attenuated influenza vaccine (LAIV) has been licensed in Europe since 2010. LAIV has been recommended preferentially in some countries such as the UK because of reported higher effectiveness compared with traditional inactivated vaccines, evidence of cross-protection against drifted strains and ease and acceptability of administration of intranasal vaccine among children and their parents and carers compared with injectable products.

The US Centers for Disease Control and Prevention (CDC) unexpectedly reported their end-of-2015/2016 season vaccine effectiveness (VE) analysis including for LAIV, finding no significant evidence of VE in children aged 2–17 years.¹ The observation was particularly marked against circulating influenza A(H1N1)pdm09, unlike the finding of significant effectiveness of inactivated influenza vaccine (IIV) in the same age group.¹ These results were presented at the US Advisory Committee on Immunization Practice (ACIP) meeting on 22 June 2016, which made a temporary recommendation that LAIV use should be suspended for the 2016/2017 influenza season in the USA.¹ The decision was further reviewed at the ACIP meeting in February 2017.

The CDC results together with those from the US Department of Defence (DoD), however, seemed to be discordant with the findings from several other

LAIV VE studies undertaken in a range of settings where LAIV had also been used in children in 2015/2016, namely the UK, Finland and Canada,^{2–4} but also an AstraZeneca/MedImmune-funded study in the USA.^{5,6} These latter studies all showed evidence of good overall LAIV effectiveness, although relatively lower, in several instances, for the A(H1N1)pdm09 component of the live attenuated vaccine, compared with the IIV. For influenza A(H3N2) and B, LAIV has shown similar or better levels of effectiveness compared with IIV.^{2,4} This paper looks at possible explanations for these findings and examines what might be the implications for other national programmes and the future of the LAIV concept in general.

BACKGROUND ABOUT LAIV

Following live influenza vaccine use in Russia in the 1969 season, the first trivalent LAIVs were licensed in Russia in the 1970s based on a cold-adapted A/Leningrad/134/47/57 (H2N2) strain and continued in use across the 1980s.⁷ Cold-adapted LAIV has been licensed for use in children and adults in the USA since 2003,⁸ where the Master Donor Virus for the product manufactured by AstraZeneca/MedImmune is based on an A/Ann Arbor/6/60(H2N2) construct. LAIV was initially recommended for individuals 5–49 years old and latterly 2–49 years old in the USA. Until recently, a preferential recommendation for LAIV was in place for children.¹

Following the development and use of a monovalent live attenuated A(H1N1)pdm09 pandemic vaccine in 2009 in the USA, AstraZeneca/MedImmune trivalent seasonal LAIV (LAIV3) was used until 2013/2014. In 2013/2014, an A(H1N1)pdm09-dominated season, CDC found evidence of reduced LAIV3 VE against the circulating A(H1N1)pdm09 strain.⁹ Following this signal, CDC examined data from 2010/2011, when A(H1N1)pdm09 was one of the circulating strains, and confirmed the reduced effectiveness of LAIV3 against A(H1N1)pdm09.¹⁰ Data from 2009/2010, however, provided evidence of effectiveness against this strain for the monovalent LAIV vaccine.¹¹

After 2013/2014, CDC and AstraZeneca/MedImmune postulated that the reduced effectiveness of LAIV might be due to a thermostability issue with the A(H1N1)pdm09 vaccine strain component (A/California/7/2009(H1N1)pdm09-like virus), possibly combined with vaccine handling issues.^{12,13} Based on this theory, AstraZeneca/MedImmune replaced the LAIV3



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A(H1N1)pdm09 A/California vaccine strain with an A/Bolivia/559/2013 strain, which is antigenically A/California-like, but was intended to be more thermostable. This new strain was included in the AstraZeneca/MedImmune quadrivalent LAIV (LAIV4) vaccine product used in 2015/2016 in both North America and Europe. The IIVs used in 2015/2016 in the Northern hemisphere across North America and Europe still contain the original A/California/7/2009 strain.

US FINDINGS IN 2015/2016

The provisional results of the CDC end-of-season influenza VE analysis for the 2015/2016 season, which was dominated by circulation of influenza A(H1N1)pdm09, were presented to the ACIP on 22 June 2016. In children, 2–17 years of age, an overall LAIV4 VE of 3% (non-significant) and –21%

(non-significant) against A(H1N1)pdm09 compared with 63% (significant) and 65% (significant) for IIV, respectively, was reported (figure 1).¹⁵

Similar preliminary results were reported in a US DoD study undertaken in 2015/2016. In children, 2–17 years of age, the authors found an LAIV4 VE against A(H1N1)pdm09 infection of 15% (non-significant) compared with 68% (significant) for IIV in children (figure 1).¹⁵

Provisional data from an AstraZeneca/MedImmune-sponsored study Influenza Clinical Investigation for Children (ICICLE), however, which overlaps with some of the same geographical areas as the CDC study in 2015/2016, showed apparently discordant findings using the same test negative case-control (TNCC) design. This study reported an LAIV4 VE of 50% (non-significant) against A(H1N1)pdm09 confirmed infection. This compares with

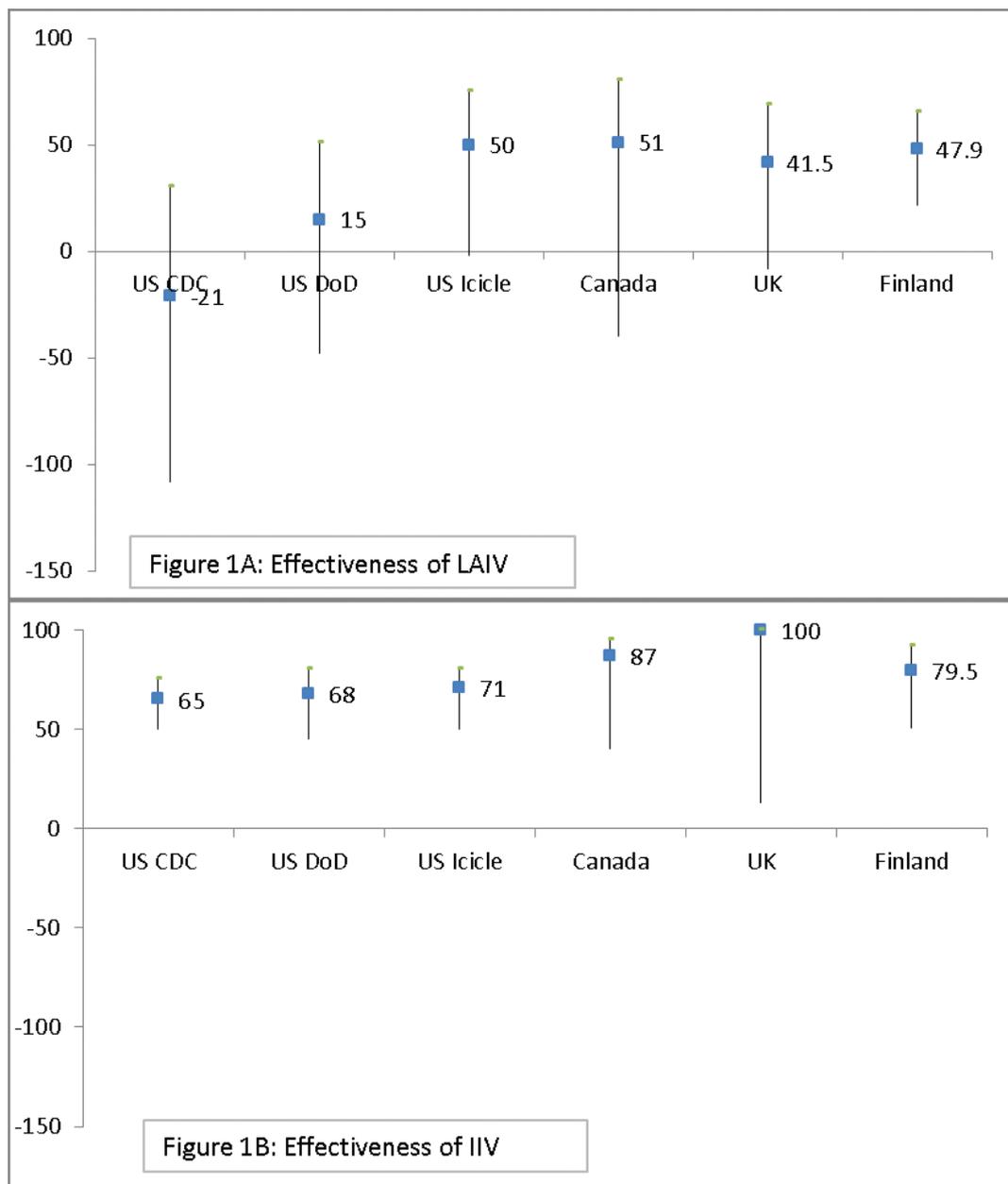


Figure 1 Summary of paediatric vaccine study sites and vaccine effectiveness findings for LAIV and IIV against A(H1N1)pdm09 for 2015/2016 in North America and Europe in children 2–17 years of age in 2015/2016 (in Finland, 2 and 3 years old only). All studies used test negative case-control design except the Finland study (population cohort). (A) Effectiveness of LAIV, (B) effectiveness of IIV. CDC, Centers for Disease Control and Prevention; DoD, Department of Defence; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.

an IIV VE in children of 71% (significant) against A(H1N1)pdm09 (figure 1).^{5,6}

OTHER LAIV PROGRAMMES

In Europe, AstraZeneca/MedImmune LAIV3 was registered for use by the European Medical Agency for children 2–17 years of age in 2010. The UK introduced LAIV3 for children in 2013/2014 following modelling that predicted that the vaccination of healthy children 2–16 years of age would be a highly cost-effective intervention due to the projected direct effect of preventing influenza infection in children, but also by reducing the rate of infection in children, who are the main spreaders of influenza, providing indirect protection to vulnerable members of the population.¹⁴ In the first year of the programme, all healthy children 2 and 3 years of age were offered a single dose of LAIV through primary care. A series of geographically discrete pilots, where children of primary school age were offered LAIV3 in a variety of settings (in particular through schools, pharmacies and primary care), were also conducted in England.¹⁵ The following season in 2014/2015, the national programme extended to all children 4 years of age using LAIV4, with a continuation of the primary school age pilots, with some areas also offering LAIV4 to children in the first 2 years of secondary school.¹⁶ Finally, in 2015/2016, the LAIV4 national programme was extended to all children of school years 1 and 2 (5 and 6 years of age), together with a continuation of the primary school age pilot area programme.¹⁷ Across the same seasons similar arrangements were in place in Wales, but in Scotland and Northern Ireland all children aged 2–11 years have been offered LAIV4 from 2014/2015 onwards.¹⁸

As part of the UK programme roll-out, a study was undertaken to evaluate both the direct effectiveness of influenza vaccine in children across the UK and its potential population-level impact by comparing the epidemiology of influenza in those areas of England where children of school age were offered vaccine to those areas of the country where they were not.

Over the period 2013/2014 until 2015/2016, the UK experienced similar seasons to those in the USA, with activity dominated by circulation of A(H1N1)pdm09, then by drifted A(H3N2) and then A(H1N1)pdm09, respectively, together with influenza B each season.^{18–20}

The UK end-of-season 2015/2016 VE results, however, appear discordant with the findings from the US CDC, where similar methods to estimate VE against laboratory-confirmed influenza infection have been used. In children 2–17 years of age, LAIV4-adjusted VE in the UK was 57% overall (significant), 41.5% (non-significant) for A(H1N1)pdm09 and 81.4% (significant) for influenza B. These findings compare with estimates of 100% (significant) and 56.3% (non-significant) for IIV effectiveness against A(H1N1)pdm09 and B, respectively, in children.² Similar results were seen for protection against influenza-confirmed hospitalisation in both England and Scotland.^{21 22}

Over the three seasons since the UK paediatric programme began, the overall LAIV VE for laboratory-confirmed influenza infection in primary care in the UK was 53.1% (significant) against all confirmed influenza, compared with a VE of 31.5% (non-significant) for IIV. The LAIV VE showed evidence of significant VE against both laboratory-confirmed A(H3N2) and influenza B infection, with moderate although non-significant effectiveness against A(H1N1)pdm09. In comparison over the 3-year period, there was no evidence of significant effectiveness of IIV against influenza B or A(H3N2), but there was significant effectiveness of 100% against A(H1N1)pdm09.²

In addition, there was evidence of the population impact of offering vaccine to all primary school-age children in pilot areas (where uptake of >50% was achieved in target groups each season) when compared with non-pilot areas in England. This was seen in both lower rates of general practitioner influenza-like illness consultations and influenza-confirmed hospitalisations in both 2013/2014 and 2014/2015 in targeted and non-targeted age-groups.^{23 24} In 2013/2014, there was also evidence of a significantly lower number of primary school absences²⁵ and in influenza-related social media queries²⁶ in primary school pilot areas compared with the non-pilot areas.

Other than the USA and UK, only a small number of other countries are using LAIV produced by A-Z/MedImmune on a widespread basis. In Finland, based on a cost-effectiveness analysis,²⁷ a universal childhood influenza vaccination programme was introduced in 2006. Initially, those aged 6 months to 35 months were eligible for trivalent inactivated vaccine (TIV) free of charge, with the intention to gradually expand to the older age groups. After the A(H1N1) influenza pandemic and the safety signal of narcolepsy mostly affecting those 5–15 years of age,²⁸ TIV coverage among children 6–35 months old dropped from over 40% to 13%. To increase TIV coverage and provide access to a more effective vaccine, since the 2015–2016 season, LAIV4 has been offered as an alternative only for those 2 years of age. However, no preferential recommendation was made. To understand the impact of the two different vaccines, a population-based register linkage cohort study was undertaken in Finland in 2015/2016 when A(H1N1)pdm09 was the dominant strain. Among children 2 years of age eligible for vaccination, the LAIV4 VE was 47.9% (significant) for influenza A and 57.2% (non-significant) for B. This compares with an IIV VE of 79.5% for influenza A (significant) and -1% for influenza B (non-significant).³ It is also noteworthy that previous vaccination with TIV improved VE both for LAIV and TIV.

In Canada, where LAIV has been used in children for several years, a 2015/2016 TNCC study undertaken through the Canadian sentinel primary care network found an LAIV4-unadjusted VE of 51% (non-significant) against A(H1N1)pdm09. This compared with an IIV VE in children of 87% (significant) against A(H1N1).^{4 6} Finally, a TNCC study was undertaken in Saxony Germany in children 2–17 years old, which found lower effectiveness of LAIV compared with IIV (12% VE, 95% CI -95 to 60) versus (90% VE, 95% CI 57 to 98).²⁹

POSSIBLE EXPLANATIONS FOR THESE OBSERVATIONS

The UK, Finnish, Canadian and US AstraZeneca/MedImmune findings in 2015/2016 had higher point estimates than the CDC and DoD study, but several had non-significant estimates for LAIV effectiveness against H1N1pdm09. Many studies do show a consistent trend of lower LAIV VE for A(H1N1)pdm09 compared with IIV in a paediatric population. WHO convened an ad hoc meeting to discuss this issue and to explore what the potential explanatory factors for this observation might be.⁴ Several hypotheses were put forward relating to the studies, the vaccine itself, the population being vaccinated and the viruses that were circulating (table 1).⁵

The US observations of lack of effectiveness could be a chance finding, as all three non-US studies demonstrate an overall LAIV4 effectiveness of 40%–50% with 95% CIs that overlap with the US CDC estimate. The US finding might also represent methodological differences, for example, due to differences in vaccine ascertainment or case definition. However, the consistent CDC findings over a number of seasons and the relatively

Table 1 Potential studies to investigate reduced LAIV VE hypotheses

Hypotheses	Study approaches
CDC/DoD A/H1N1pdm09 specific finding — related to chance, methodology, programmatic issues	More highly powered vaccine effectiveness study with larger sample size in eligible population also allowing for stratification by age and/or previous exposure
Replicative fitness of the current A/H1N1pdm09 strain	Comparative shedding study of LAIV vaccinees to compare different vaccine virus formulations
Viral interference/competition between A/H1N1pdm09 vaccine strain and other vaccine viruses in multivalent formulation	In vitro and vivo challenge studies to compare viral shedding patterns
Prior vaccination with LAIV or IIV resulting in specific immunological interference with H1N1pdm09 vaccine virus replication	VE and shedding studies to compare groups with different prior vaccine exposure
Repeat LAIV vaccination resulting in broader, longer term immunological changes affecting all viruses (mimicking adult response)	Serological and cell-mediated LAIV immunity studies

CDC, Centers for Disease Control and Prevention; DoD, Department of Defence; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; VE, vaccine effectiveness.

lower effectiveness of LAIV compared with IIV for A(H1N1)pdm09 in all countries suggest that there might be a specific issue with the A(H1N1)pdm09 component of the LAIV vaccine.

One potential hypothesis is viral interference between the A(H1N1)pdm09 vaccine strain and other LAIV4 vaccine viruses in the quadrivalent vaccine product, which might affect the ability of the vaccine strain to replicate.³⁰ Indeed studies have demonstrated likely effectiveness of monovalent pandemic (H1N1)pdm09 in the US¹¹ and elsewhere,³¹ although the fact that a reduction in A(H1N1)pdm09 effectiveness was seen in 2010/2011 in the USA at a time when the trivalent LAIV vaccine was being used suggests that this is a less likely root-cause explanation.¹⁰

Another mechanism that has been postulated is that prior vaccination results in mucosal antibody interference with vaccine virus replication of LAIV, on the basis that the USA has a much longer standing influenza vaccine programme compared with European countries (including relatively high coverage of IIV in children 6–18 months of age). Initial evidence, however, suggests this explanation is unlikely. The age group-specific VE in 2015/2016 reported by CDC was lower for children 2–8 years old compared with 9–17 years old, who would be a more highly vaccinated population.³² In addition, investigations in the USA in 2013/2014 and 2015/2016 have not shown a significant difference in LAIV VE between those vaccinated and not vaccinated in the previous season.⁶ Further evidence is provided by findings from Finland, where prior influenza vaccination, including with IIV, did not lead to significantly lower VE, but rather the opposite.³

The vaccine used in the USA is obtained from the same manufacturer as the UK and Finnish LAIV programmes. Suboptimal thermostability of the A(H1N1)pdm09 A/California/7/09 strain, linked to exposure to high environmental temperature, was proposed as one of the main explanations for the reduction in VE seen in 2013/2014.¹³ Based on these observations, the A/California/7/09 strain was replaced with the A/Bolivia/559/2013 strain on the premise that it was more heat stable. On this basis, an ongoing thermostability issue is thought unlikely to explain the discordance between the US CDC and US ICICLE findings in 2015/2016.

Strain mismatch between the A/Bolivia 2015/2016 vaccine strain and circulating A(H1N1)pdm09 strains has also been raised as a potential mechanism. This explanation would seem unlikely though as antigenically the A/Bolivia/559/2013 strain remains very similar to circulating A(H1N1)pdm09 viruses.

Finally, reduced A(H1N1)pdm09 vaccine virus ability to replicate in the mammalian host has been raised as a possible hypothesis and, indeed, MedImmune/AstraZeneca has suggested this

may be a root-cause factor based on in vitro experiments.³³ This particular strain has only recently adapted to the human host and its replicative ability might be less than other influenza strains. The WHO vaccine composition group has already recommended a switch for the 2017 Southern hemisphere A(H1N1) vaccine strain to an A/Michigan/45/2015 (H1N1)pdm09-like virus, which will mean an update for the A(H1N1)pdm09 strain for the 2017/2018 Northern hemisphere vaccine.³⁴

WORK REQUIRED TO INVESTIGATE THESE FINDINGS

Further work is required to gain an understanding of the likely underlying mechanism for the apparent reduction in LAIV VE measured in observational studies in the USA compared with elsewhere, but also for the probable relative reduction in LAIV A(H1N1)pdm09 effectiveness compared with IIV. In those countries still using LAIV, a series of studies are required to determine the effectiveness of LAIV against a range of laboratory and clinical end-points and to measure VE and to explore further which explanatory factors (table 1) are most likely to explain the earlier reduction in A(H1N1)pdm09 effectiveness. Table 1 lays out potential observational and clinical studies that should be undertaken to answer these different hypotheses.

In 2016/2017, observational VE studies have been underway in both the UK and Finland. These studies are intended to provide robust estimates of LAIV VE in the target age group and to understand what role prior vaccination may have played on vaccine performance, although this most recent season has been dominated by circulation of A/H3N2. A series of clinical studies looking at viral shedding and immunogenicity, using both serological and cell-mediated end-points, are also required to address specific questions in relation to vaccine virus competition, the potential role of prior vaccination and the impact of repeated vaccination on longer term immunity. It will be critical that this work is continued for the 2017/2018 season, when the LAIV vaccine virus composition for A(H1N1)pdm09 for the Northern hemisphere will change and A(H1N1)pdm09 may circulate again. The findings from such studies will be important to inform future paediatric influenza vaccine strategy both in Europe and North America, but also pandemic vaccine planning, where live attenuated vaccines are recognised to play a potentially important role by WHO and member states,^{4,5} as shown by the recent European authorisation of pandemic influenza vaccine H5N1 for children.³⁵

FUTURE IMPLICATIONS

In the light of the US findings, the UK Joint Committee on Vaccination and Immunisation (JCVI) has recently reviewed the evaluation of the UK programme and the results from other countries. The UK

evaluation has found good overall performance of LAIV — particularly against drifted influenza A(H3N2) and B strains. In addition, the intranasally administered vaccine has been well accepted by parents and children. The JCVI concluded ‘that it would be important to continue to keep the programme under close review and monitor over the longer term. The Committee agreed it would consider any relevant new evidence and developments on the impact of the nasal spray flu vaccine as it emerges but strongly supported the continuation of this important public health programme in the UK’.³⁶ The Finnish National Immunisation Technical Advisory Group has also recommended that the LAIV roll-out continues provided the cost-effectiveness of the intervention is acceptable.

With the suspension of the US LAIV programme for 2016/2017, other countries, such as Canada and Germany, withdrew their preferential recommendation for use of LAIV. Therefore, the UK and Finland will be two of only a few countries globally that will still be using LAIV on a widespread basis. The limited use of this technology represents a potential threat to the longer term sustainability of LAIV production, and hence the importance of monitoring performance in those settings still using the vaccine. The 2016/2017 Northern hemisphere season has been dominated by A(H3N2) to date, and so will not provide immediate answers to what is the effectiveness of LAIV against A(H1N1)pdm09, highlighting the importance of enhanced surveillance in coming seasons with the future A(H1N1)pdm09 strain that is used. It is hoped that this work will assist others, such as the USA, in their decision-making around the future use of LAIV.

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