

ADDENDUM – LAIV Use in Children and Adolescents

Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI) †

Canadian Immunization Guide Chapter on
Influenza and Statement on Seasonal Influenza
Vaccine for 2016-2017

PROTECTING CANADIANS FROM ILLNESS



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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

This addendum to the Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017 has been issued to address updated recommendations regarding the use of live attenuated influenza vaccine in children 2–17 years of age.

NACI recommendation: Use of live attenuated influenza vaccine in children 2–17 years of age

After careful review of available studies from the last several influenza seasons, NACI has revised its recommendations on the use of influenza vaccine in children 2–17 years of age:

1. In children without contraindications to the vaccine, any of the following vaccines can be used: quadrivalent live attenuated influenza vaccine (LAIV), quadrivalent inactivated influenza vaccine (QIV) or trivalent inactivated influenza vaccine (TIV).
2. The current evidence does not support a recommendation for the *preferential* use of LAIV in children and adolescents 2–17 years of age.

Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used.

NACI recommendation: Need for further research to address knowledge gaps

After careful review of available studies from the last several influenza seasons, NACI has identified the need for further research to address current knowledge gaps:

3. NACI strongly encourages further multidisciplinary (e.g., epidemiological, immunological, virological) research to investigate the reasons for the discordant 2015–2016 vaccine effectiveness (VE) estimates between studies and explanations for poor LAIV effectiveness against A(H1N1)pdm09 reported in some studies.
4. NACI strongly recommends that sufficient resources be provided to enhance influenza-related research and sentinel surveillance systems in Canada to improve the evaluation of influenza vaccine efficacy and effectiveness to provide the best possible evidence for Canadian influenza vaccination programs and recommendations.

Live attenuated influenza vaccine

FluMist® Quadrivalent is a live attenuated influenza vaccine manufactured by MedImmune (a subsidiary of AstraZeneca) for administration by intranasal spray, and authorized for use for persons 2–59 years of age in Canada. The influenza strains in FluMist® Quadrivalent are attenuated so that they do not cause influenza and are cold-adapted and temperature sensitive, so that they replicate in the nasal mucosa, rather than in the lower respiratory tract.

The trivalent formulation of LAIV received a Notice of Compliance from Health Canada in June 2010 and was first used in publicly funded immunization programs in Canada for the 2012–2013 influenza season. The quadrivalent formulation was approved for use in Canada for the 2014–2015 season and has been in use since that time. The trivalent vaccine is no longer available in Canada.

Previous NACI recommendations

In 2011, NACI recommended the preferential use of LAIV in children and adolescents 2–17 years of age who did not have contraindications to the vaccine. This recommendation was based upon randomized placebo controlled studies and post-marketing safety data.¹ These studies showed LAIV to be safe, efficacious, and immunogenic in children and to provide better protection against influenza than TIV in children (NACI Recommendation Grade A). In 2013, NACI's recommendation was updated to indicate that there was evidence for the preferential use of LAIV in young children (younger than 6 years of age), based on superior efficacy of LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I). It was anticipated that the superior efficacy of LAIV over TIV extended beyond 6 years of age, but the evidence did not indicate at which specific age the efficacies of LAIV and TIV might have become equivalent nor at which age LAIV efficacy may have become inferior to that of TIV.²

Sources of vaccine effectiveness data

Subsequent data on LAIV VE have come primarily from American studies.³⁻¹⁶ Only the United States Influenza Vaccine Effectiveness Network (US Flu VE Network) has consistently reported LAIV VE over the past several influenza seasons (2010–2016) in children and adolescents 2–17 years of age.³⁻⁶ The Influenza Clinical Investigation for Children (ICICLE) study, conducted by MedImmune as part of its four season (until 2017) post-marketing commitment to the US Food and Drug Administration (FDA), has VE data available for the 2013–2014 through 2015–2016 influenza seasons for children and adolescents 2–17 years of age.⁸⁻¹⁰ The US Department of Defense (DoD) has published LAIV VE data for US Air Force dependants (2–17 years of age) for the 2013–2014 and 2015–2016 influenza seasons^{5,7} and active military personnel for the 2010–2011 through 2013–2014 influenza seasons.¹¹⁻¹⁴ These American studies used the test-negative design.³⁻¹⁴ The American Household Influenza Vaccine Effectiveness (HIVE) study, using an alternative household cohort design, investigated LAIV and inactivated influenza vaccine (IIV) VE in children (2–8 years of age) and adolescents (9–17 years of age) for the 2012–2013 and 2013–2014 seasons.^{15,16}

Data on LAIV VE from outside of the United States of America (USA) have come from the Canadian Sentinel Practitioner Surveillance Network (SPSN) for 2013–2014 and 2015–2016,^{17,18} Germany for the 2012–2013 season,¹⁹ the United Kingdom (UK) sentinel surveillance network for the 2013–2014 through the 2015–2016 seasons,²⁰⁻²² and Finland for the 2015–2016 season.²³ These LAIV VE studies were mostly of test-negative design,¹⁷⁻²² with one prospective cohort study.²³

Vaccine effectiveness

Influenza seasons 2010–2011, 2011–2012, and 2012–2013

Overall, studies in children and adolescents (2–17 years of age) report moderate and statistically significant (lower bound of the 95% confidence interval does not include zero) trivalent LAIV vaccine effectiveness against any influenza virus, influenza A(H3N2) and influenza B for the 2010–2011 through 2012–2013 influenza seasons.^{3,19} The US Flu VE Network reported that the vaccine effectiveness estimates for LAIV and IIV were comparable (with overlapping confidence intervals) and statistically significant against any influenza, influenza A(H3N2) and influenza B viruses during the 2010–2011 and 2012–2013 influenza seasons, and against any influenza and A(H3N2) in the 2011–2012 season (sample sizes were too small to estimate vaccine effectiveness against influenza B virus in this season).³ The German study also reported a high and statistically significant vaccine effectiveness estimate for

LAIV against any influenza in the 2012–2013 influenza season.¹⁹ In contrast, the US Flu VE Network observed LAIV to have had a low and statistically non-significant (confidence interval includes zero) vaccine effectiveness against A(H1N1) compared to a high and statistically significant vaccine effectiveness estimate for IIV against A(H1N1) in the 2010–2011 influenza season (vaccine effectiveness of LAIV and IIV against A(H1N1) was not estimated in the 2011–2012 or 2012–2013 influenza seasons due to limited sample size).³

Influenza season 2013–2014

During the 2013–2014 influenza season in which influenza A(H1N1) was dominant, all three American test-negative studies (US Flu VE Network, DoD and ICICLE) reported low to negative and statistically non-significant vaccine effectiveness estimates for quadrivalent LAIV against any influenza and against A(H1N1).^{6,8} In contrast, the reported vaccine effectiveness of IIV was moderately high and statistically significant against any influenza and against influenza A(H1N1) (US Flu VE Network and ICICLE). The American HIVE study found moderately high, but statistically non-significant LAIV and IIV VE estimates against influenza A(H1N1) in children (2–8 years of age).¹⁶ Investigations by the manufacturer concluded the reduced effectiveness seen in the USA may have been due to the A/California/7/2009(H1N1)pdm09-like LAIV strain's being vulnerable to heat degradation, which may have occurred during distribution.¹⁰

NACI subsequently concluded that heat degradation was unlikely to have been an issue in Canada for the 2013–2014 season due to strict temperature control and monitoring throughout transport.²⁴ NACI further noted that vaccine effectiveness estimates for the trivalent LAIV formulation used in Canada were higher than those seen in the American studies for the 2013–2014 season.¹⁷ Data from the Canadian SPSN reported a high and statistically significant unadjusted vaccine effectiveness estimate for LAIV against any influenza, with a high but statistically non-significant unadjusted vaccine effectiveness estimate against A(H1N1). Both point estimates were comparable to those of IIV, but based on small sample sizes with wide confidence intervals.¹⁷ In light of these findings, NACI continued to recommend preferential use of LAIV in children and adolescents, but with a commitment to continue to monitor LAIV vaccine effectiveness in future seasons.^{24,25} Although also limited in sample size, a Canadian cluster randomized clinical trial conducted in children and adolescents in the 2013–2014 influenza season found better performance of LAIV compared to IIV.²⁶

As a result of the concerns regarding thermostability that followed the investigation into the poor LAIV VE against influenza A(H1N1) in the USA, the manufacturer replaced the A/California/7/2009(H1N1)pdm09-like strain with an antigenically similar strain (A/Bolivia/559/2013) with improved thermostability for the 2015–2016 season.

Influenza season 2014–2015

The 2014–2015 influenza season was dominated by antigenically drifted A(H3N2) viruses. Two American studies (US Flu VE Network and ICICLE)^{4,10} and the UK sentinel surveillance network study²² reported low to negative and statistically non-significant LAIV and IIV vaccine effectiveness estimates against any influenza and against influenza A(H3N2) (with the exception of the ICICLE study which reported a low but statistically significant vaccine effectiveness estimate for IIV against A(H3N2)⁹). No LAIV vaccine effectiveness estimates were available for A(H1N1). The predominance of antigenically drifted A(H3N2) viruses was proposed as an explanation for the estimates of reduced vaccine effectiveness against A(H3N2) generally; higher vaccine effectiveness was observed against less prevalent vaccine-like A(H3N2) viruses in the USA⁴ and also with IIV in Canada.²⁷

Influenza season 2015–2016

In the 2015–2016 influenza season with predominant circulation of influenza A(H1N1), moderate and statistically significant LAIV vaccine effectiveness against any influenza (46–58%) was observed among children and adolescents 2–17 years of age in two American studies (DoD and ICICLE),^{5,9} the UK,²⁰ and a cohort study conducted by the Finland National Institute for Health and Welfare.²³ In unadjusted analysis by the Canadian SPSN, LAIV effectiveness against any influenza (74%) was also statistically significant but with wide confidence intervals.¹⁸ However, in contrast, the US Flu VE Network found a low, non-statistically significant LAIV vaccine effectiveness against any influenza (3%).⁵ All four studies with both LAIV and IIV vaccine effectiveness data (US Flu VE Network, DoD, ICICLE, and the Finland study) reported lower vaccine effectiveness point estimates for LAIV compared to IIV for any influenza, but only the US Flu VE Network showed a statistically significant difference (non-overlapping confidence intervals) between LAIV and IIV.^{5,9,23} In unadjusted analysis, the Canadian SPSN reported comparable point estimates for LAIV (74%) and IIV (63%) effectiveness against any influenza, but with wide and overlapping confidence intervals.¹⁸

In A(H1N1) specific analysis, two of the five studies that used the test-negative design (ICICLE and Canadian SPSN) found comparable but statistically non-significant LAIV vaccine effectiveness estimates of approximately 50%, again with wide confidence intervals.^{9,18} Two other American studies based on the test-negative design (US Flu VE Network, DoD) reported lower LAIV vaccine effectiveness estimates (-21%, 15%) with confidence intervals overlapping zero that were more consistent with no vaccine protection.⁵ The point estimates of vaccine effectiveness against A(H1N1) for LAIV were lower than for IIV in all four studies (ICICLE, DoD, US Flu VE Network, Canadian SPSN), but only the US Flu VE Network reported a significantly lower LAIV estimate (non-overlapping confidence intervals). The UK study vaccine effectiveness estimates against influenza A(H1N1) are not currently publicly available. The study from Finland using a prospective cohort design did not generate subtype specific vaccine effectiveness estimates.

LAIV vaccine effectiveness against A(H3N2) was only reported in one study (DoD), which found a statistically non-significant, moderate vaccine effectiveness estimate.⁵

Decisions regarding LAIV use for 2016–2017 in other jurisdictions

Based upon the US Flu VE Network data showing that LAIV provided no protective benefit during the influenza A(H1N1) dominant 2015–2016 influenza season and no evidence of effectiveness against the dominant circulating strains in the two prior influenza seasons (2013–2014 and 2014–2015), the American Advisory Committee on Immunization Practices (ACIP) recommended during its June 2016 meeting that LAIV should not be used during the 2016–2017 influenza season.²⁸ LAIV continues to be recommended for use in children in the UK and Finland for the 2016–2017 season.²⁹ Studies conducted in both of these countries, and in Canada, found a statistically significant overall protective effect of LAIV in children for 2015–2016, although sample sizes limit the precision of those estimates.^{18,20,23} The US FDA has also determined that specific regulatory action for LAIV is not necessary at this time, following a review of manufacturing and clinical data supporting licensure and the totality of evidence presented at the June 2016 ACIP meeting, and continues to find that the benefits of quadrivalent LAIV outweigh any potential risks.³⁰ Quadrivalent LAIV remains licensed for use in the USA. The FDA's determination was made taking into account the limitations of observational studies in estimating VE and the seasonal variability of influenza VE.

NACI recommendations

After careful review of the available vaccine effectiveness data over the last several influenza seasons, NACI concludes that the current evidence is consistent with LAIV's providing comparable protection against influenza to that afforded by IIV in various jurisdictions. Previous studies and clinical experience also indicate LAIV to be a safe vaccine. NACI, therefore, recommends that in children without contraindications to the vaccine, any of the following vaccines can be used: quadrivalent live attenuated influenza vaccine (LAIV), quadrivalent inactivated influenza vaccine (QIV) or trivalent inactivated influenza vaccine (TIV). The current evidence does not support a recommendation for the *preferential* use of LAIV in children 2–17 years of age. However, the observational study data reviewed highlight the challenge in interpreting LAIV and IIV vaccine effectiveness when point estimates by influenza subtype are derived based on small sample sizes associated with wide confidence intervals. Therefore, in making its recommendation, NACI recognizes the need to continue to monitor LAIV VE data closely by influenza subtype and the relative effectiveness of LAIV compared to IIV.

Knowledge gaps

The reasons for the discordant 2015–2016 vaccine effectiveness estimates between studies are currently unknown, but may reflect biological mechanisms methodological issues or both, such as biases in the design of observational study, as well as statistical (sample size) considerations limiting the precision of vaccine effectiveness estimates. Possible explanations for poor LAIV effectiveness against A(H1N1) in some studies include changes in the serological profile of the population post pandemic A(H1N1), higher population levels of pre-existing antibody interference with vaccine virus replication, potential competitive interference with viral replication among live viruses in the quadrivalent vaccine, and suboptimal performance of the new A/Bolivia/559/2013(H1N1) LAIV component for reasons that have yet to be identified. As a consequence of these gaps in scientific knowledge, NACI strongly encourages further, multidisciplinary (e.g., epidemiological, immunological, virological) research in this area.

Influenza vaccination is recommended for all individuals in Canada aged 6 months or older who do not have contraindications to the vaccines licensed for use. Therefore, annual influenza vaccination represents a large, ongoing public health investment. The evaluation of seasonal influenza vaccines and of public health influenza programs relies on research studies and sentinel surveillance systems with sufficient sample sizes to generate vaccine efficacy and effectiveness estimates, such as by age, vaccine type and administration history, influenza subtype, and genetic sequence. Therefore, NACI strongly recommends that sufficient resources be provided to enhance influenza-related research and sentinel surveillance systems in Canada. This enhanced research would improve the evaluation of influenza vaccine efficacy and effectiveness and, therefore, better inform Canadian influenza vaccination program recommendations and optimize the results of this significant investment.

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