

# NACI Opinion on LAIV Effectiveness in Young Children

## Background

The National Advisory Committee on Immunization (NACI) has been asked for an opinion on the effectiveness of live attenuated influenza vaccine (LAIV) in children in light of recent data in the United States of America (USA) related to the 2013-2014 influenza season, and particularly whether NACI maintains its preferential recommendation for LAIV in children for the 2014-2015 season.

## Recent findings and recommendations in the United States of America:

Three separate studies have been carried out in the USA to assess the vaccine effectiveness (VE) of live attenuated and inactivated influenza vaccines in children for the 2013-2014 influenza season. These studies were conducted by:

- The Flu Vaccine Effectiveness Network (CDC and contributors);
- MedImmune (manufacturer of LAIV); and
- The American Armed Forces in Air Force families .

All three studies used the test-negative case-control design and found similar results: low to negative and non-statistically significant VE for the LAIV in children 2 to 17 or 18 years of age. In contrast, VE for inactivated vaccines was moderate to high and statistically significant. In relative efficacy analyses, the inactivated vaccine was favored compared to LAIV in 2013-2014 in children and the result was statistically significant.

When the data are further analyzed by influenza virus strain, the LAIV was effective against the B strain in children in 2013-2014. However, VE against the H1N1 strain was low and the confidence intervals overlapped the null effect, and therefore are not statistically significant. In the USA, from Flu VE network data that were presented to NACI, the H1N1 VE was analyzed when combining the 2011-2012, the 2012-2013 and the 2013-2014 seasons' data; however in the first 2 years, there were very few cases of H1N1. In contrast, the H1N1 strain was largely predominant in the 2013-2014 influenza season. The H3N2 strain was not assessed in 2013-2014 because there were too few cases during that season.

The manufacturer is investigating the possibility that the low to negative VE estimates are associated with certain shipment dates of the vaccine. Their study findings to date suggest that there was a positive and statistically significant VE estimate against the H1N1 strain in children for vaccine received outside the shipment dates of concern. These findings showed the adjusted LAIV H1N1 vaccine effectiveness by shipment group was minus 49% for vaccine shipped during weeks 4-9 (the confidence interval overlaps zero and the results are not statistically significant) and 83% for earlier or later shipments of vaccine (statistically significant and the confidence interval range is above zero). The manufacturer is therefore exploring vaccine handling processes to explain this unexpected finding.

It is important to highlight that the data showing low or negative and non-significant effectiveness of LAIV in children apply only to the 2013-2014 US studies and only for the H1N1 strain. [The Advisory Committee on Immunization Practices](#) (ACIP) reviewed these data at their October 29th 2014 meeting and continues to recommend LAIV preferentially in healthy children 2 to 8 years old . The [American Academy of Pediatrics](#) (AAP) does not preferentially recommend LAIV, but recommends that, “[LAIV] should be considered for *healthy* children 2 through 8 years of age who have no contraindications or precautions to the intranasal vaccine. If LAIV is not readily available, inactivated influenza vaccine (IIV) should be used; vaccination should not be delayed to obtain LAIV.”



## Recent findings in Canada

The low to negative VE for LAIV (not-statistically significant) found in the US studies was not seen in Canadian surveillance data for the 2013-14 season, based on information from the Canadian Sentinel Influenza Vaccine Effectiveness Surveillance Network (SPSN) [D. Skowronski, personal communication, 2014 November 20]. However, it is important to note some differences in the Canadian context:

- During the 2013-2014 influenza season, Canada used a trivalent formulation of LAIV, unlike the USA that used a quadrivalent formulation. Both of these formulations are manufactured by the same company in the same plants, but the assembly process for the strains differs. Handling may also differ given that the different formulations were destined for different countries and clients.
- The number of cases less than 20 years old within SPSN receiving the trivalent LAIV (the formulation used in Canada) was very small, and the findings need to be interpreted with caution and in context with all available evidence.

## Ongoing investigations

It is known that VE can vary by age group, season, influenza strain, and product. The finding of the apparent lack of effectiveness against H1N1 infections for LAIV during the 2013-14 season in the USA was unexpected as previous studies of LAIV, including from the CDC Flu VE Network, have suggested superior vaccine effectiveness compared to inactivated influenza vaccine, primarily in children 2 to 6 years old. However, the 2013-14 influenza season was the first season since the 2009 pandemic where H1N1 was the predominant circulating strain.

Investigations are still underway in the USA to determine possible reasons for this finding, including:

- A unique event;
- A study methods or analysis issue (the studies are observational by design);
- A vaccine stability or lot issue;
- A supply chain cold chain issue; or
- An alternate explanation.

Additional studies are underway. For example, the manufacturer is further analyzing their hypothesis related to shipment dates and the CDC is planning additional surveillance for the 2014-2015 season. Also of interest is one publication that discusses the possibility that the H1N1pdm09 strain may be less stable than other H1N1 LAIV viruses due to specific sequences in the HA stalk . NACI will review additional information as it arises.

## 2014-15 Influenza Season

To date, data from [FluWatch](#), Canada's national surveillance system that monitors the spread of influenza and influenza-like illnesses, has indicated a greater circulation of influenza A(H3N2) and influenza B viruses than H1N1 . As of Week 01 (January 4 to January 10, 2015), 97% of influenza detections have been influenza A, and the vast majority of those subtyped have been A(H3), with the elderly being disproportionately affected. Strain characterization by the National Microbiology Laboratory in Canada and the CDC have also identified drifted influenza A(H3N2) strains from the H3N2 vaccine virus.

As noted in the [2014-2015 Seasonal Influenza Statement](#) , *FluWatch* collects data and information from various sources to provide a national picture of influenza activity. Each of the different data sources contribute to a fuller understanding of the epidemiology of the influenza season. However, the data sources capture a very small proportion of the influenza infections that take place in Canada each year, and each has a bias towards certain ages, severity, people with co-morbidities, et cetera. Consequently, the current surveillance systems are not sufficiently robust to detect and analyze differences in vaccine effectiveness between two vaccine products in specific age groups as would be beneficial to provide some clarity regarding a similar situation in the future.

## NACI opinion

At present **there is no change to the existing NACI recommendations for LAIV in children** in light of the following:

- The LAIV formulations used in the US and Canada in 2013-2014 were different.
- The VE issue occurred in only one season and with one strain of influenza.
- The low to negative and non-significant LAIV effectiveness seen in the American studies has not been detected in Canada.
- Further information is needed to understand the apparent lack of effectiveness against H1N1 infections for LAIV in young children during the 2013-14 season in the USA and studies are ongoing.
- The studies that were done in the USA are observational. NACI has based its preferential recommendation for LAIV in children on randomized controlled trials and observational data.
- In the American Flu VE network data from 2011-2012 and 2012-2013, the relative efficacy of LAIV vs. inactivated vaccines favours LAIV in children 2-8 years old.
- Surveillance data show that influenza A(H3N2) is the predominant circulating strain for the 2014-2015 season, followed by influenza B, with very little circulating influenza A(H1N1) so far, and LAIV has been shown to offer good protection against influenza A(H3N2) and influenza B, against drifted strains as well, which may be occurring for the H3N2 strain this season.
- NACI is monitoring this issue and will review additional information as it arises.

Recommendations may change as new information becomes available.

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Footnote \*\* In the 2014-15 influenza statement, NACI recommends preferential use of LAIV, where available, in young children (younger than 6 years of age) based on superior efficacy of LAIV compared to TIV, with weaker evidence of superior efficacy in older children. It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. If LAIV is not available for those for whom it is considered superior, TIV should be used.

[Top of Page](#)



## References