



Summary of the NACI Seasonal Influenza Vaccine Statement for 2018–2019

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Abstract

Background: There are many different influenza vaccines authorized for use in Canada and new evidence on influenza and vaccines is emerging all the time. The National Advisory Committee on Immunization (NACI) provides recommendations annually regarding seasonal influenza vaccines to the Public Health Agency of Canada (PHAC).

Objective: To summarize the NACI recommendations regarding the use of seasonal influenza vaccines for the 2018–2019 influenza season in light of two NACI reviews conducted on 1) the risk of serious influenza-related complications in children and adults with neurologic and neurodevelopment conditions and 2) the efficacy/effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older.

Methods: For both topics, NACI's Influenza Working Group developed a predefined search strategy to identify all eligible studies, assessed their quality, summarized and analyzed the findings, proposed recommendations and identified the Grade of evidence that supported them. In light of the evidence, the recommendations were then considered and approved by NACI.

Results: NACI concludes there is fair evidence to recommend that children and adults with neurologic and neurodevelopment conditions are groups for whom influenza immunization is particularly recommended (Evidence Grade B recommendation). On choosing influenza vaccines for persons 65 years of age and older, at a programmatic level, NACI recommends that any of the four influenza vaccines available for use should be used. There is insufficient evidence to make a comparative recommendation on the use of these vaccines at a programmatic level (Grade I). At an individual level, NACI recommends that high-dose trivalent inactivated influenza vaccine (TIV) should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and quadrivalent inactivated influenza vaccine over standard-dose TIV (Grade I).

Conclusion: NACI continues to recommend annual influenza vaccination for all individuals aged six months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, people who provide essential community services and people in direct contact during culling operations with poultry infected with avian influenza.

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Introduction

Together, influenza and pneumonia are ranked among the top 10 leading causes of death in Canada (1). Although the burden of influenza can vary from year to year, it is estimated that, in a given year, there are an average of 12,200 hospitalizations related to influenza (2) and approximately 3,500 deaths (3). The National Advisory Committee on Immunization (NACI) provides annual recommendations regarding seasonal influenza vaccines to the Public Health Agency of Canada (PHAC).

For the 2018–2019 influenza season, NACI developed recommendations regarding the use of seasonal influenza vaccines in light of two reviews. The reviews examined 1) the risk of serious influenza-related complications in children and adults with neurologic and neurodevelopment conditions (NNCs) and 2) the efficacy/effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older. Complete details can be found in the *Statement*

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on *Seasonal Influenza Vaccine for 2018–2019* (4) and related publications. The objective of this article is to summarize this annual seasonal influenza statement.

Methods

In the preparation of the *Statement on Seasonal Influenza Vaccine for 2018–2019*, NACI's Influenza Working Group (IWG) followed NACI's evidence-based process for developing recommendations. The IWG identified and reviewed evidence relating to the two literature reviews and, following the review and analysis of this information, the IWG proposed recommendations (5). The NACI critically appraised the available evidence and approved the specific recommendations brought forward.

Neurologic or neurodevelopment conditions

The review of evidence utilized a rapid review approach, whereby elements of a full systematic review process were modified due to time and resource limitations, but the modified process remained rigorous and transparent. The NNCs were defined as neuromuscular, neurovascular, neurodegenerative, neurodevelopment conditions and seizure disorders (and, for children, included febrile seizures and isolated developmental delay), but excluded migraines and psychiatric conditions without neurological conditions.

A predefined search strategy was used to search two electronic databases (MEDLINE and EMBASE) from inception to October 25, 2016 for studies relating to the risk of serious influenza-related complications in children and adults with NNCs. After removal of duplicates, a single reviewer screened (title, abstract and full-text) studies retrieved from the database searches for potential eligibility. Hand-searching of the reference lists of a random subset of included studies was also conducted to identify additional relevant publications. One reviewer extracted data from eligible studies into an evidence table using a piloted data abstraction template and a second reviewer independently validated the abstracted data, with any disagreements or discrepancies resolved by discussion and consensus. The methodological quality of included studies was assessed independently by two reviewers using the design-specific criteria by Harris et al., which was adopted by NACI for rating the internal validity of individual studies (6).

A narrative synthesis of the extracted information was used to explore overall patterns in the data, including similarities and differences by age group (children and adults), influenza type (pandemic and seasonal) and outcome (emergency department presentation, hospitalization, intensive care unit [ICU] admission, respiratory failure, need for mechanical ventilation and death).

Efficacy and effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older

Five electronic databases (MEDLINE, EMBASE, Global Health, ProQuest Public Health Database and Scopus) were searched using separate search strategies for Fluzone® High-Dose (June 1, 2014 to March 22, 2017) and Fludac® (January 1, 2012 to March 22, 2017) adapted from the previously conducted NACI review, *A Review of the Literature of High Dose Seasonal*

Influenza Vaccine for Adults 65 Years and Older (7). These literature search updates were performed with at least one year of overlap with the last searches for literature related to the efficacy and effectiveness of these vaccines. After removal of duplicates, two reviewers independently screened (title, abstract and full-text) studies retrieved from the database searches for potential eligibility. Hand-searching of the reference lists of included studies and any secondary research articles identified in the database search was performed to identify additional relevant publications. One reviewer extracted data from eligible studies into an evidence table using a piloted data abstraction template. A second reviewer independently validated the abstracted data, with any disagreements or discrepancies resolved by discussion and consensus. The methodological quality of included studies was assessed independently by two reviewers using the design-specific criteria by Harris et al., which was adopted by NACI for rating the internal validity of individual studies (6).

A narrative synthesis of the extracted information was used to explore overall patterns in the data, including summaries of the direction, size and statistical significance of reported effect estimates for various study-defined outcomes.

Results

Neurologic or neurodevelopment conditions

The evidence related to the risk of serious influenza-related complications in adults and children with NNCs came mostly from descriptive studies (i.e., case series), which are generally considered of lower quality (level III evidence); therefore, the findings should be interpreted with consideration of the increased potential for confounding factors and bias from these types of studies. In addition, some studies lacked clarity in the conditions that constituted NNCs and there was also a lack of consistency across studies with the specific NNCs investigated. However, the body of evidence is suggestive of a relatively high burden of pre-existing NNCs in adults and children who had experienced serious pandemic influenza A(H1N1) pdm09- and seasonal influenza-related complications, such as hospitalization, ICU admission and death. Of the individuals with at least one study-defined risk factor for influenza-related complications, 12%–17% of adults and 24%–26% of children hospitalized for pandemic or seasonal influenza had NNCs as a risk factor. Similarly, of individuals with at least one study-defined risk factor for influenza-related complications, approximately 18% of adults admitted to the ICU with pandemic influenza and 40% of children admitted to the ICU with pandemic or seasonal influenza had NNCs as a risk factor. Of individuals with at least one study-defined risk factor for influenza-related complications, almost 25% of adults who died from pandemic influenza infection and 58%–62% of children who died from pandemic or seasonal influenza infection had NNCs as a risk factor.

There is also consistent evidence from this mostly descriptive body of evidence to suggest that pre-existing NNCs increase the risk for serious influenza-related complications; for example, neurologic conditions and seizure disorder in children and neuromuscular conditions in adults were identified as statistically significant risk factors for influenza-related hospitalization. Among those hospitalized for influenza infection, neurologic, neurodevelopment and neuromuscular conditions in children



and neurologic and neurocognitive conditions in adults were identified as statistically significant risk factors for ICU admission. Similarly, among children hospitalized for influenza infection, neurologic conditions were identified as a statistically significant risk factor for death. There was limited evidence identified for other serious influenza-related complications in this population, such as emergency department presentation, respiratory failure and the need for mechanical ventilation.

The findings of this rapid review of the literature are consistent with previous preliminary evidence reviewed by NACI indicating that children and adults with NNCs are at risk for influenza-related complications and hospitalization.

Therefore, based upon current evidence and expert opinion, NACI concludes there is fair evidence to recommend that children and adults with neurologic and neurodevelopmental conditions are groups for whom influenza immunization is particularly recommended (NACI Evidence Grade B Recommendation).

The NACI recommendation remains consistent with international bodies, including the United States Centers for Disease Control and Prevention, the United Kingdom's Joint Committee on Vaccination and Immunisation and the Australian Technical Advisory Group on Immunization, all of which have listed both children and adults with neurologic conditions as a high-risk group for influenza complications.

Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Literature Review on Individuals with Neurologic or Neurodevelopment Conditions and Risk of Serious Influenza-Related Complications* (8).

Efficacy and effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older

The updated literature search identified five studies that assessed the effectiveness of Fluzone High-Dose in adults 65 years of age and older: two studies providing supplementary analysis to a previously published randomized controlled trial (RCT); two retrospective cohort studies; and a multicentre, cluster RCT. Four observational studies were identified in the updated literature review that assessed the effectiveness of Flud in this population. Observational studies, which comprise the majority of the studies identified in the updated review, may be susceptible to residual confounding, selection bias and other biases that may complicate the interpretation of effectiveness estimates. Therefore, these methodological limitations should be considered when interpreting the current body of efficacy and effectiveness evidence for Fluzone High-Dose and Flud.

Findings from the newly identified studies suggest that Fluzone High-Dose is significantly more effective than standard-dose vaccine in preventing influenza-like illness, all-cause hospitalization, serious cardiorespiratory events possibly related to influenza and non-laboratory confirmed influenza-related death. Studies to date have not shown high-dose vaccine to be more effective than standard-dose vaccine in preventing hospitalization for influenza or pneumonia, all-cause mortality or functional decline; however, there is some evidence to suggest that current season vaccination with Fluzone High-Dose is

likely to provide clinical benefit over standard-dose vaccine, irrespective of vaccination received in the previous season (high-dose or standard-dose vaccine). The updated review also found some further evidence that Fluzone High-Dose may provide additional benefit over standard dose vaccine in the very elderly, but further studies are needed to validate this purported age effect.

The observational studies identified provide some additional evidence that Flud vaccination of adults 65 years of age and older provides clinical benefit against hospitalization for influenza or pneumonia and for laboratory-confirmed influenza infection compared with no vaccination. The potential added benefit of using the MF59-adjuvanted vaccine over unadjuvanted vaccines could not be assessed in these studies due to either a lack of a comparison against an unadjuvanted vaccine or to methodological or sample size limitations.

Previously noted evidence gaps have not been addressed by the newly identified studies; there remain no studies that directly compare high-dose vaccine with MF59-adjuvanted vaccine or compare either of these trivalent inactivated influenza vaccines (TIVs) with quadrivalent inactivated influenza vaccines (QIVs).

Based on updated reviews of the literature on the efficacy and effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older, NACI has concluded that there is no substantial change in the conclusions to be drawn from the scientific literature; however, NACI has updated its recommendation on the choice of vaccine product for this age group by creating programmatic-level (i.e., provinces and territories making decisions for publicly funded immunization programs) and individual-level (i.e., individuals wishing to prevent vaccine-preventable disease or a clinician wishing to advise individual patients) recommendations.

At a programmatic level, NACI recommends that any of the four influenza vaccines available for use in adults 65 years of age and older should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV, and QIV. High-dose TIV is expected to provide superior protection compared to standard-dose TIV; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy and effectiveness between high-dose TIV, MF59-adjuvanted TIV, and QIV, there is insufficient evidence to make a comparative recommendation on the use of these vaccines at the programmatic level (Grade I).

At an individual level, NACI recommends that high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older. NACI concludes that, given the burden of disease associated with influenza A(H3N2) and the good evidence of better efficacy compared to standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and QIV over standard-dose TIV (Grade I).

Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Literature Review Update on the Efficacy and Effectiveness of High-Dose (Fluzone® High-Dose) and MF59-Adjuvanted (Flud®) Trivalent Inactivated Influenza Vaccines in Adults 65 Years of Age and Older* (9).



Summary of NACI recommendations for the use of influenza vaccines for the 2018–2019 influenza season

NACI continues to recommend influenza vaccination for all individuals aged six months and older who do not have contraindications to the vaccine, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk of complications and others as indicated in **Table 1**.

Table 1: Groups for whom influenza vaccination is particularly recommended

<p>People at high risk of influenza-related complications or hospitalization</p> <ul style="list-style-type: none"> All pregnant women^a Adults and children with the following chronic health conditions: <ul style="list-style-type: none"> cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma) diabetes mellitus and other metabolic diseases cancer, immune compromising conditions (due to underlying disease, therapy or both) renal disease anemia or hemoglobinopathy neurologic or neurodevelopment conditions^b morbid obesity (body mass index [BMI] of 40 and over) children and adolescents (age six months to 18 years) undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye syndrome associated with influenza People of any age who are residents of nursing homes and other chronic care facilities People 65 years of age and older All children 6– 59 months of age Indigenous peoples <p>People capable of transmitting influenza to those at high risk</p> <ul style="list-style-type: none"> Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized): <ul style="list-style-type: none"> household contacts of individuals at high risk, as listed in the section above household contacts of infants under 6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine members of a household expecting a newborn during the influenza season Those providing regular child care to children 59 months of age and under, whether in or out of the home Those who provide services within closed or relatively closed settings to persons at high risk (e.g., crew on a ship) <p>Others</p> <ul style="list-style-type: none"> People who provide essential community services People in direct contact during culling operations with poultry infected with avian influenza

^a The risk of influenza-related hospitalization increases with length of gestation (i.e., it is higher in the third than in the second trimester)

^b These neurologic or neurodevelopmental conditions include neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders (and for children, include febrile seizures and isolated developmental delay), but exclude migraines and psychiatric conditions without neurological conditions

Recommended influenza vaccine options by specific age and risk groups and by dosage and route of administration by age are summarized in **Tables 2 and 3**, respectively.

Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)^a

Recipient by age group	Vaccine types available for use	Comments
Children 6–23 months of age	<ul style="list-style-type: none"> TIV QIV Adjuvanted TIV 	As TIV, QIV and adjuvanted TIV are authorized for this age group NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.
Children 2–17 years of age	<ul style="list-style-type: none"> TIV QIV Quadrivalent LAIV 	<p>In children without contraindications to the vaccine, any of the following vaccines can be used: LAIV; QIV; or TIV.</p> <p>The current evidence does not support a recommendation for the <i>preferential</i> use of LAIV in children and adolescents 2–17 years of age.</p> <p>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.</p> <p>LAIV is contraindicated for children with immune compromising conditions.</p> <p>LAIV, TIV or QIV can be used in children with chronic health conditions and without contraindications (see the <i>Contraindications and Precautions</i> (Section II) and <i>Choice of vaccine product for children 2 to 17 years of age</i> (Section V) sections of the Statement for more details) (4).</p>
Adults 18–59 years of age	<ul style="list-style-type: none"> TIV QIV Quadrivalent LAIV 	<p>TIV and QIV are the recommended products for adults with chronic health conditions.</p> <p>TIV and QIV, instead of LAIV, are recommended for health care workers.</p> <p>LAIV is contraindicated for adults with immune compromising conditions.</p>
Adults 60–64 years of age	<ul style="list-style-type: none"> TIV QIV 	TIV and QIV are authorized for use in this age group.
Adults 65 years of age and older	<ul style="list-style-type: none"> TIV QIV Adjuvanted TIV High-dose TIV 	<p>At the programmatic level, NACI recommends that any of the four influenza vaccines available for use in adults 65 years of age and older should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV, and QIV. High-dose TIV is expected to provide superior protection compared to standard-dose TIV; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy/effectiveness between high-dose TIV, MF59-adjuvanted TIV, and QIV, there is insufficient evidence to make a comparative recommendation on the use of these vaccines at the programmatic level (Grade I).</p> <p>At the individual level, NACI recommends that high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older. NACI concludes that, given the burden of disease associated with influenza A(H3N2) and the good evidence of better efficacy compared to standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and QIV over standard-dose TIV (Grade I).</p>
Pregnant women	<ul style="list-style-type: none"> TIV QIV 	LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine.

Abbreviations: LAIV, live attenuated influenza vaccine (quadrivalent formulation); QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine

^a Updated recommendations noted in **bold**



Table 3: Recommended influenza vaccine dosage and route, by age, for the 2018–2019 influenza season

Age group	TIV without adjuvant ^a (Intramuscular)	QIV without adjuvant ^b (Intramuscular)	TIV without adjuvant, high dose (Fluzone [®] High-Dose) (Intramuscular)	MF59- adjuvanted TIV (Fluad Pediatric [®] or Fluad [®]) (Intramuscular)	LAIV (FluMist [®] Quadrivalent) (Intranasal)	Number of doses required
6–23 months	0.5 mL ^c	0.5 mL ^c	N/A	0.25 mL	N/A	1 or 2 ^d
2–8 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1 or 2 ^d
9–17 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	0.5 mL	N/A	N/A	N/A	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.5 mL	N/A	1

Abbreviations: LAIV, live attenuated influenza vaccine (quadrivalent formulation); N/A, not applicable; QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine

^a Influvac[®] three years and older, Fluviral[®] six months and older, Agriflu[®] six months and older

^b Flulaval[®] Tetra six months and older, Fluzone Quadrivalent six months and older

^c This information may differ from the product monograph. Published and unpublished evidence suggest moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines (10,11). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to *Statement on Seasonal Influenza Vaccine for 2011–2012* (12)

^d Children six months to less than nine years of age who have never received the seasonal influenza vaccine require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children under nine years of age who have properly received one or more doses of seasonal influenza vaccine in the past should receive one dose per influenza vaccination season thereafter

Conclusion

The NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization, including the following: all pregnant women; people capable of transmitting influenza to those at high risk; people who provide essential community services; and people in direct contact during culling operations with poultry infected with avian influenza. For the 2018–2019 influenza season, NACI has reaffirmed its recommendation regarding the inclusion of children and adults with neurologic and neurodevelopmental conditions as being at increased risk for influenza-related complications and hospitalization. The Statement also provides updated recommendations on the use of a high-dose inactivated split virion vaccine (Fluzone High-Dose, Sanofi Pasteur) and an MF59-adjuvanted inactivated subunit vaccine (Fluad, Seqirus) in persons 65 years of age and older.

Authors' statement

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Conflict of interest

None.

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