Summary of the National Advisory Committee on Immunization (NACI) Seasonal Influenza Vaccine Statement for 2021–2022

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Abstract

Background: Several influenza vaccines are authorized in Canada and the evidence on influenza immunization is continually evolving. The National Advisory Committee on Immunization (NACI) provides recommendations regarding the use of seasonal influenza vaccines annually to the Public Health Agency of Canada (PHAC).

Objective: To summarize NACI recommendations regarding the use of seasonal influenza vaccines for 2021–2022 and to highlight new recommendations.

Methods: Annual influenza vaccine recommendations are developed by NACI’s Influenza Working Group for consideration and approval by NACI. The development of the recommendations is based on the NACI evidence-based process.

Results: The following new recommendations were made: 1) Influvac® Tetra may be considered as an option among the standard dose quadrivalent inactivated influenza vaccines (IIV4-SD) offered to adults and children three years of age and older; 2) Fluzone High Dose Quadrivalent (IIV4-HD) may be considered an option for individuals 65 years of age and older who are currently recommended to receive Fluzone® High Dose (trivalent); and 3) Flucelvax® Quad may be considered amongst the quadrivalent influenza vaccines offered to adults and children nine years of age and older for annual influenza immunization. Guidance for use of influenza immunizations during the coronavirus disease 2019 pandemic is also highlighted.

Conclusion: NACI continues to recommend that an age-appropriate influenza vaccine should be offered annually to anyone six months of age and older who does not have contraindications to the vaccine. Vaccination should be offered as a priority to 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.

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Introduction

Seasonal influenza is an infectious viral illness that occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children (1). Epidemics of seasonal influenza occur annually in Canada, generally in the late fall and winter months; however, the burden of influenza illness can vary from year to year. Current information on influenza activity globally can be found on the World Health Organization’s FluNet website (2) and nationally on the Public Health Agency of Canada’s (PHAC) FluWatch website (3).

The National Advisory Committee on Immunization (NACI) provides PHAC with annual recommendations regarding the use of seasonal influenza vaccines, which reflect identified changes in influenza epidemiology, immunization practices and influenza

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vaccine products authorized and available for use in Canada. The development of the annual influenza vaccine recommendations, which is led by the NACI Influenza Working Group (IWG), involves a thorough review and evaluation of the literature as well as discussion and debate at the scientific and clinical practice levels on a variety of issues, which can include the following: the burden of influenza illness and the target populations for vaccination, efficacy, effectiveness, immunogenicity and safety of influenza vaccines, vaccine schedules, and other aspects of influenza immunization. Issues related to ethics, equity, feasibility and acceptability are also systematically examined by NACI for comprehensive development of vaccine guidance (4).

The objective of this article is to provide a concise summary of NACI's recommendations and supporting information for the 2021–2022 influenza season, including conclusions from reviews of evidence on 1) a new, biosimilar, egg-based, quadrivalent inactivated influenza vaccine (Influvac® Tetra; IIV4-SD), 2) a new quadrivalent, egg-based high dose inactivated influenza vaccine (Fluzone® High Dose Quadrivalent; IIV4-HD), and 3) a mammalian cell culture-based influenza vaccine (Flucelvax® Quad; IIV4-cc). Complete details can be found on the PHAC website in the NACI Advisory Committee Statement: Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2021–2022 (the Statement) (5) and related publications.

### Influenza vaccine abbreviations

Updated abbreviations used by NACI to describe the defining features of various types of influenza vaccines are presented in Table 1.

**Methods**

In the preparation of the 2020–2021 seasonal influenza vaccine recommendations, NACI's IWG identified the need for evidence reviews for new topics, and then reviewed and analyzed the available evidence, and proposed new or updated recommendations according to the NACI evidence-based process for developing recommendations (6). For a more detailed explanation of the strength of NACI recommendations and the grading of evidence refer to Appendix Table A1. A published, peer-reviewed framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix) was applied to ensure that issues related to ethics, equity, feasibility and acceptability were systematically assessed and integrated into guidance (4).

For the 2020–2021 influenza season, the IWG reviewed evidence regarding the use of two new vaccines: 1) Influvac Tetra, a new biosimilar, egg-based, quadrivalent inactivated influenza vaccine; and 2) Fluzone High Dose (HD) Quadrivalent an egg-based high dose quadrivalent inactivated influenza vaccine (IIV4). Influvac Tetra (IIV4-SD) was first authorized for use in Canada in adults in March 2019 and subsequently in children three years of age and older in February 2020. Fluzone High Dose (HD) Quadrivalent was first authorized for use in Canada in adults in June 2020. A trivalent formulation, Fluzone High-Dose, was previously authorized for use in adults 65 years of age and older in Canada, and recommended by NACI, but marketing of the vaccine was discontinued as of February 2021. Following the review and

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### Table 1: National Advisory Committee on Immunization (NACI) influenza vaccine abbreviations

| Influenza vaccine category | Formulation | Type | Current NACI abbreviation* |
|---------------------------|-------------|------|---------------------------|
| Trivalent (IIV3)          | Standard dose®, unadjuvanted, IM administered, egg-based | IIV3-SD |
| Inactivated influenza vaccine (IIV) | Standard dose®, unadjuvanted, IM administered, egg-based | IIV4-SD |
| Quadrivalent (IIV4)       | Standard dose®, unadjuvanted, IM administered, cell culture-based | IIV4-cc |
|                           | High dose®, unadjuvanted, IM administered, egg-based | IIV4-HD |
| Live attenuated influenza vaccine (LAIV) | Unadjuvanted, Nasal spray, egg-based | LAIV3 |
|                           | Unadjuvanted, Nasal spray, egg-based | LAIV4 |

Abbreviations: IIV, inactivated influenza vaccine; IIV3, trivalent inactivated influenza vaccine; IIV3-Adj, adjuvanted egg-based trivalent inactivated influenza vaccine; IIV3-HD, high-dose egg-based trivalent inactivated influenza vaccine; IIV3-SD, standard-dose egg-based trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine; IIV4-cc, standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV4-HD, high-dose egg-based quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose egg-based quadrivalent inactivated influenza vaccine; IIV4-cc, standard-dose cell culture-based quadrivalent inactivated influenza vaccine; LAIV3, egg-based trivalent live attenuated influenza vaccine; LAIV4, egg-based quadrivalent live attenuated influenza vaccine; NACI, National Advisory Committee on Immunization

* The numeric suffix denotes the number of antigens contained in the vaccine (“3” refers to the trivalent formulation and “4” refers to the quadrivalent formulation). The hyphenated suffix “-SD” is used when referring to IIV products that do not have an adjuvant, contain 15 µg HA per strain and are administered as a 0.5 mL dose by intramuscular injection; “-cc” refers to an IIV product that is made from influenza virus grown in cell cultures instead of chicken eggs (Flucelvax® Quad); “-Adj” refers to an IIV with an adjuvant (IIV3-Adj for Fluarix® or Fluarix Pediatric®); and “-HD” refers to an IIV that contains higher antigen content than 15 µg HA per strain (IIV3-HD for Fluzone® High-Dose or IIV4-HD for Fluzone® High-Dose Quadrivalent)

1 15 µg HA per strain
2 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain
3 60 µg HA per strain

Source: Table reproduced from NACI Seasonal Influenza Vaccine Statement for 2021–2022 (5)
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Recommendations and supporting evidence on the use of mammalian cell culture-based, inactivated seasonal influenza vaccine (Flucelvax Quad) from the NACI Supplemental Statement – Mammalian Cell Culture-Based Influenza Vaccines (7) were also incorporated into the Statement on Seasonal Influenza Vaccine for 2021–2022. Flucelvax Quad is the first and only available mammalian cell culture-based inactivated seasonal influenza vaccine in Canada; it was first authorized for use in adults and children nine years of age and older on November 22, 2019. The IWG oversaw the completion of a systematic review to inform the development of guidance on the use of Flucelvax Quad (IIV4-cc). Six electronic databases (EMBASE, MEDLINE, Scopus, ProQuest Public Health and ClinicalTrials.gov) were searched from inception until February 12, 2019, using a predefined search strategy to identify relevant literature on the efficacy, effectiveness, immunogenicity and safety in adults and children four years of age and older. Registered clinical trials and grey literature from international public health authorities and National Immunization Technical Advisory Groups were also considered. Additionally, hand-searching of the reference lists of included articles was performed by one reviewer to identify additional relevant publications. Two reviewers independently screened the titles and abstracts of records retrieved from the search and eligible full-text articles for inclusion. One reviewer extracted data from eligible studies and appraised the methodological quality of these studies using the criteria outlined by Harris et al. (8). A second reviewer independently validated the data extraction and quality assessment. A narrative synthesis of the extracted data was performed. NACI provided new recommendations based on assessment of the evidence.

Results

Use of seasonal influenza vaccine in the presence of the novel coronavirus disease 2019 (COVID-19)

In light of the ongoing coronavirus disease 2019 (COVID-19) pandemic, PHAC, in consultation with NACI and the Canadian Immunization Committee, has developed the following additional guidance on the delivery of influenza vaccination programs and administration of seasonal influenza vaccine to support provincial and territorial vaccine programs and primary care providers during the COVID-19 pandemic for 2021–2022:

- Guidance for Influenza Vaccine delivery in the presence of COVID-19 (9)
- Guidance on the use of seasonal influenza vaccine in the presence of COVID-19 (10)

This guidance is based on currently available scientific evidence and expert opinion. The content will be reviewed regularly, and updates will be made as necessary throughout the upcoming influenza season as the public health context evolves and new evidence and policy issues emerge.

New egg-based quadrivalent influenza vaccine

NACI concluded that Influvac Tetra is safe and has non-inferior immunogenicity to the trivalent Influvac formulation. Therefore, NACI recommended that Influvac Tetra may be considered among the standard dose quadrivalent inactivated influenza vaccines (IIV4-SD) offered to adults and children three years of age and older (Discretionary NACI Recommendation).

New egg-based high dose quadrivalent influenza vaccine

NACI concluded that Fluzone High Dose Quadrivalent is comparably safe and has non-inferior immunogenicity to the previously authorized trivalent Fluzone High Dose formulation. Therefore, NACI has issued the following discretionary individual-level recommendation on the use of Fluzone High Dose Quadrivalent (IIV4-HD): For individuals 65 years of age and older whom are currently recommended to receive Fluzone High Dose (trivalent), NACI recommends that Fluzone High Dose Quadrivalent (IIV4-HD) may be considered as an option (Discretionary NACI Recommendation). Recommendations for public health programs remain unchanged at this time.

Inclusion of mammalian cell culture-based quadrivalent influenza vaccine

The peer-reviewed published evidence on the effectiveness, immunogenicity and safety of IIV4-cc manufactured using fully cell-derived viruses was sparse. The systematic review identified four observational studies (11–14) investigating the vaccine effectiveness of IIV4-cc compared with egg-based IIV and two peer-reviewed randomized controlled trials that assessed the immunogenicity and safety of IIV4-cc compared with different IIV3-cc formulations (produced using the same Madin-Darby Canine Kidney [MDCK] cell culture-based manufacturing process). There was evidence indicating that IIV4-cc may be more effective than egg-based IIV3 and IIV4 influenza vaccines against non-laboratory confirmed influenza-related outcomes, including influenza-related health care interactions and influenza-like-illness (ILI). Although some data suggest that IIV4-cc may be more effective against laboratory-confirmed influenza A(H3N2) virus infection than egg-based IIV, there was no consistent and statistically significant difference in effectiveness identified for adults or children vaccinated with IIV4-cc compared with egg-based IIV. Two studies that assessed the immunogenicity and safety of IIV4-cc compared with different IIV3-cc formulations (produced by Seqirus using the same MDCK cell culture-based manufacturing process) were identified in this review (15,16). There was also evidence indicating that IIV4-cc has a comparable...
immunogenicity and safety profile to egg-based influenza vaccines already licensed in Canada and the trivalent formulation of this cell culture-based influenza vaccine that has been licensed in the United States and Europe, but for which licensure has never been sought in Canada (17–22).

Based on assessment of the available pre-licensure and post-market clinical trial and observational data, NACI concluded that IIV-cc is an effective, safe, well-tolerated and immunogenic alternative to conventional egg-based influenza vaccines for children and adults. Therefore, NACI has made the following recommendation, supplementing NACI’s overarching recommendation for influenza vaccination, which is available in the NACI Seasonal Influenza Vaccine Statement (5):

NACI recommends that Flucelvax Quad may be considered among the IIV4 offered to adults and children nine years of age and older (Discretionary NACI Recommendation).

• NACI concludes that there is fair evidence to recommend vaccination of adults and children nine years of age and older with Flucelvax Quad (Grade B Evidence)

For complete details of this review, rationale, relevant considerations and additional information supporting this recommendation, refer to the NACI Supplemental Statement: Mammalian Cell Culture-Based Influenza Vaccines (7). Notably, Flucelvax Quad was recently authorized by Health Canada for use in adults and children two years of age and older. This updated authorized age indication supersedes the information for Flucelvax Quad found in relevant sections within the NACI Statement on Seasonal Influenza Vaccine for 2021–2022 (5). Further details are available in the new product monograph for this vaccine (23).

Summary of National Advisory Committee on Immunization recommendations for the use of influenza vaccines for the 2021–2022 influenza season

NACI continues to recommend influenza vaccination to anyone six months and older who does not have contraindications to the vaccine. Vaccination should be offered as a priority to 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 List 1.

Recommended influenza vaccine options by age group and by dosage and route of administration by age are summarized in Table 2 and Table 3, respectively.

List 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization
• All children 6–59 months of age
• Adults and children with the following chronic health conditions*:
  o Cardiac or pulmonary disorders (includes bronchopulmonary dysplasia, cystic fibrosis, and asthma)
  o Diabetes mellitus and other metabolic diseases
  o Cancer, immune compromising conditions (due to underlying disease, therapy, or both, such as solid organ transplant or hematopoietic stem cell transplant recipients)
  o Renal disease
  o Anemia or hemoglobinopathy
  o Neurologic or neurodevelopment conditions (includes neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions, and seizure disorders [and, for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions)
  o Morbid obesity (body mass index of 40 and over)
  o Children six months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye’s syndrome associated with influenza
• All pregnant women
• People of any age who are residents of nursing homes and other chronic care facilities
• Adults 65 years of age and older
• Indigenous peoples

People capable of transmitting influenza to those at high risk
• 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
• Household contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated:
  o Household contacts of individuals at high risk
  o Household contacts of infants less than six months of age, as these infants are at high risk but cannot receive influenza vaccine
  o Members of a household expecting a newborn during the influenza season
• Those providing regular child care to children 0–59 months of age, whether in or out of the home
• Those who provide services within closed or relatively closed settings to people at high risk (e.g. crew on a ship)

Others
• People who provide essential community services
• People who are in direct contact with poultry infected with avian influenza during culling operations

* Refer to Immunization of Persons with Chronic Diseases and Immunization of Immunocompromised Persons in Part 3 of the Canadian Immunization Guide for additional information about vaccination of people with chronic diseases (24). Source: List reproduced from NACI Seasonal Influenza Vaccine Statement for 2021–2022 (5)
Table 2: Recommendations on choice of influenza vaccine type for individual- and public health program-level decision-making by age group

| Recipient by age group | Vaccine types authorized for use | Recommendations on choice of influenza vaccine |
|------------------------|---------------------------------|-----------------------------------------------|
| 6–23 months            | IIV3-SD* IIV3-Adj IIV4-SD       | • A quadrivalent influenza vaccine licensed for this age group should be used in infants and young children without contraindications, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine.  
  • If a quadrivalent vaccine is not available, any of the available trivalent vaccines licensed for this age group should be used. |
| 2–17 yearsb            | IIV3-SD* IIV4-SD IIV4-cc (nine years of age and over) LAIV4 | • An age appropriate IIV4-SD, LAIV4, or IIV4-cc (IIV4-cc only authorized for nine years of age and older) should be used in children without contraindications, including those with non-immune compromising chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine.  
  o There are currently no IIV4-cc vaccines licensed for children younger than nine years of age.  
  • LAIV4 may be given to children with:  
  o Stable, non-severe asthma  
  o Cystic fibrosis who are not being treated with immunosuppressive drugs (e.g. prolonged systemic corticosteroids)  
  o Stable HIV infection, if the child is currently being treated with HAART and has adequate immune function  
  • LAIV should not be used in children for whom it is contraindicated for, such as those with:  
  o Severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing)  
  o Medically attended wheezing in the seven days prior to vaccination  
  o Current receipt of aspirin or aspirin-containing therapy  
  o Immune compromising conditions, with the exception of stable HIV infection, i.e. if the child is treated with HAART (for at least four months) and has adequate immune function  
  • LAIV is contraindicated in pregnant adolescents. IIV4-SD or IIV4-cc should be used instead.  
  • If IIV4-SD, IIV4-cc, and LAIV4 are not available, IIV3-SD should be used. |
| 18–59 years            | IIV3-SD* IIV4-SD IIV4-cc LAIV4  | • Any of the available influenza vaccines should be used in adults without contraindications.  
  o There is some evidence that IIV may provide better efficacy than LAIV in healthy adults  
  • LAIV is not recommended for the following:  
  o Pregnant women  
  o Adults with any of the chronic health conditions identified in List 1, including immune compromising conditions  
  o Healthcare workers |
| 60–64 years            | IIV3-SD* IIV4-SD IIV4-cc       | Any of the available influenza vaccines should be used in those without contraindications. |
| 65 years and oldera    | IIV3-SD* IIV3-Adj IIV3-HD* IIV4-SD IIV4-cc | * IIIV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older.  
  o Other than a recommendation for using IIV-HD over IIV-SD formulations, NACI has not made comparative individual-level recommendations on the use of the other available vaccines in this age group. In the absence of a specific product, any of the available age appropriate influenza vaccines should be used. |

| Individual-level decision-making | Public health program-level decision-making |
|----------------------------------|---------------------------------------------|
| • IIIV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older.  
  o Other than a recommendation for using IIV-HD over IIV-SD formulations, NACI has not made comparative individual-level recommendations on the use of the other available vaccines in this age group. In the absence of a specific product, any of the available age appropriate influenza vaccines should be used. |
| • Any of the available influenza vaccines should be used.  
  o There is insufficient evidence on the incremental value of different influenza vaccines (i.e. cost-effectiveness assessments have not been performed by NACI) to make comparative public health program-level recommendations on the use of the available vaccines. |

Abbreviations: HAART, highly active antiretroviral therapy; IIV, inactivated influenza vaccine; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4-cc, quadrivalent mammalian cell-culture based inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; NACI, National Advisory Committee on Immunization

* IIV3-SD formulations will not be available for use in Canada during the 2021-2022 influenza season
* Refer to Table 4 of the NACI Seasonal Influenza Vaccine Statement for 2021–2022 for a summary of vaccine characteristics of LAIV compared with IIV in children 2–17 years of age
* IIV4-cc is currently authorised for use in adults and children nine years of age and older
* IIV4-cc is currently authorized for use in adults and children nine years of age and older (5)
* IIV3-HD formulations will not be available for use in Canada during the 2021-2022 influenza season
* Refer to Table 5 of the NACI Seasonal Influenza Vaccine Statement for 2021–2022 for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older (5)
* Source: Table reproduced from the NACI Seasonal Influenza Vaccine Statement for 2021–2022 (5)
Conclusion

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. For the 2021–2022 influenza season, NACI newly recommends that Influvac Tetra and Flucelvax Quad may be considered as options among the quadrivalent inactivated influenza vaccines offered to adults and children for their annual vaccination. NACI also newly recommends that Fluzone High-Dose Quadrivalent may be considered as an option for adults 65 years of age and older.

In addition, people capable of transmitting to high-risk individuals, people who provide essential community services and people in direct contact during culling operations with poultry infected with avian influenza are particularly recommended to receive the influenza vaccine.

Authors’ statement

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Competing interests

None.

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## Appendix

### Table A1: Ratings for strength of National Advisory Committee on Immunization (NACI) recommendations and grade of evidence

| Strength of NACI recommendation based on factors not isolated to strength of evidence (e.g. public health need) | Strong | Discretionary |
|---------------------------------------------------------------------------------------------------------------|--------|---------------|
| **Wording**                                                                                                    | “should/should not be offered” | “may be considered” |
| **Rationale**                                                                                                   | Known/anticipated advantages outweigh known/anticipated disadvantages (“should”), OR known/anticipated disadvantages outweigh known/anticipated advantages (“should not”) | Known/anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists |
| **Implication**                                                                                                 | A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present | A discretionary recommendation may be considered for some populations/individuals in some circumstances Alternative approaches may be reasonable |
| **Grade of evidence based on assessment of the body of evidence**                                               | A: good evidence to recommend B: fair evidence to recommend C: conflicting evidence, however other factors may influence decision-making D: fair evidence to recommend against E: good evidence to recommend against I: insufficient evidence (in quality or quantity), however other factors may influence decision-making |