



# Summary of the NACI Supplemental Statement on Mammalian Cell Culture-Based Influenza Vaccines

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## Abstract

**Background:** Mammalian cell culture-based technology is an innovative technique for influenza vaccine manufacturing that may be a valuable alternative to overcome some of the problems and vulnerabilities associated with conventional egg-based influenza vaccine production. Flucelvax<sup>®</sup> Quad (Seqirus, Inc.) is the first and only mammalian cell culture-based quadrivalent inactivated, subunit influenza vaccine (IIV4-cc) authorized for adult and pediatric use in Canada. The National Advisory Committee on Immunization (NACI) has not previously made a recommendation on cell culture-based influenza vaccines in any population.

**Objective:** To review the available evidence for the efficacy, effectiveness, immunogenicity, and safety of IIV4-cc, and to summarize the NACI recommendation regarding the use of Flucelvax Quad in Canada in adults and children.

**Methods:** A systematic literature review on the vaccine efficacy, effectiveness, immunogenicity and safety of IIV4-cc in persons four years of age and older was performed. The systematic review's methodology was specified *a priori* in a written protocol. The NACI evidence-based process was used to assess the quality of eligible studies, summarize and analyze the findings, and develop a recommendation regarding the use of Flucelvax Quad in adults and children. The proposed recommendation was then considered and approved by NACI in light of the available evidence.

**Results:** Thirteen eligible studies were included in the evidence synthesis. In the four observational studies that assessed vaccine effectiveness of IIV4-cc, there were some data indicating potentially improved protection against influenza compared to conventional egg-based quadrivalent inactivated influenza vaccines (IIV4) or trivalent inactivated influenza vaccine (IIV3), particularly against A(H3N2) virus infection. There was also some evidence that IIV4-cc may be more effective than egg-based trivalent or quadrivalent influenza vaccines against non-laboratory confirmed influenza-related outcomes, but there is insufficient evidence for laboratory-confirmed outcomes. Two randomized controlled trials assessed the immunogenicity and safety of IIV4-cc compared with mammalian cell culture-based trivalent inactivated, subunit influenza vaccine (IIV3-cc). The IIV4-cc was well-tolerated and the reported solicited local and systemic adverse events were generally mild to moderate in intensity, self-limited and did not precipitate sequelae. One clinical review of cases and six peer-reviewed randomized controlled trials (four in adults and two in children) that reported on the safety of IIV3-cc were included in the review. The evidence on immunogenicity and safety was consistent across these studies and showed that there was no significant difference in adults and children four years of age and older who had received IIV3-cc or an egg-based IIV3.

**Conclusion:** NACI concluded that there is fair evidence (Grade B Evidence) that Flucelvax Quad is effective, safe, and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults and children nine years of age and older. 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).

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**Keywords:** National Advisory Committee on Immunization, NACI, mammalian, cell culture, MDCK, influenza vaccine

## Introduction

Influenza vaccine production using mammalian cell culture-based technology is an innovative technique that may offer enhanced manufacturing scalability, sterility, timeliness and flexibility and, thus, may be a valuable alternative to overcome some of the problems and vulnerabilities associated with conventional egg-based production (1–4). Influenza A(H3N2) viruses can undergo changes that decrease antigenic relatedness to wild-type, circulating viruses when they are grown in eggs, and that certain egg-adaptive mutations may negatively affect the immunogenicity, efficacy and effectiveness of standard egg-based influenza vaccines, especially during influenza A(H3N2)-dominant seasons (4–10). Cell culture-based influenza vaccines, solely derived from cell culture-based candidate vaccine viruses (CVVs), are insulated from such egg-adaptive changes and have the potential to provide enhanced protection in some seasons compared to standard egg-based influenza vaccines (1,4,5). Flucelvax Quad (Seqirus, Inc.) is the first and only available mammalian cell culture-based quadrivalent inactivated, subunit influenza vaccine (IIV4-cc) to be authorized for use in Canada in adults and children nine years of age and older (11). Since the vaccine first became available, the Flucelvax quadrivalent formulation (licensed as Flucelvax Quadrivalent or Flucelvax® Tetra in other jurisdictions) has been prepared from viruses propagated in mammalian cell lines (proprietary 33016-PF Madin-Darby Canine Kidney [MDCK] cell lines) adapted to grow freely in suspension in culture medium. However, prior to the 2019–2020 influenza season, some of the CVVs provided to the manufacturer had been originally derived in eggs. The Flucelvax quadrivalent formulation for the 2019–2020 influenza season was the first to be manufactured using CVVs for all four influenza viruses that were derived solely from mammalian cell lines from the initial virus isolation through to the full manufacture of the vaccine, making the vaccine egg-free (2).

The National Advisory Committee on Immunization (NACI) has not previously made a recommendation on cell culture-based influenza vaccines in any population. The objective of this advisory committee statement is to review the evidence for efficacy, effectiveness, immunogenicity, and safety that is available for Flucelvax Quad, and to provide provincial and territorial health authorities and health care professionals with guidance on its use in adults and children.

## Methods

A systematic literature review on the vaccine efficacy, effectiveness, immunogenicity and safety of IIV4-cc in persons four years of age and older was performed. Mammalian cell culture-based influenza vaccines have been approved for use by the United States (US) Food and Drug Administration in adults and children four years and older since the 2013–2014 influenza season for the last six years and effectiveness, immunogenicity and safety data is currently available for this age group.

The systematic review's methodology was specified *a priori* in a written protocol that included review questions, search strategy, inclusion and exclusion criteria and quality assessment. NACI's Influenza Working Group (IWG) reviewed and approved the protocol. A search strategy based on the objective was developed in consultation with a federal Reference Librarian from the Health Library of Health Canada and the Public Health Agency of Canada. Searches were restricted to primary research studies and case reports published in English or French, in the EMBASE, MEDLINE, Scopus, ProQuest Public Health and ClinicalTrials.gov electronic databases from inception until February 12, 2019. Registered clinical trials and grey literature from international public health authorities and National Immunization Technical Advisory Groups were also considered.

Two reviewers independently screened the titles and abstracts and eligible full-text articles.

Studies were included if they met the following criteria:

1. The study population or subpopulation consisted of individuals four years of age and older
2. Study assessed efficacy and effectiveness, immunogenicity, or safety of Flucelvax Quad or safety of Flucelvax
3. Primary research studies from peer-reviewed scientific literature
4. Case reports and case series
5. Registered clinical trials and grey literature from international public health authorities
6. The study was published in English or French

Studies were excluded if they met one or more of the following criteria:

1. The study did not present data on any of: efficacy, effectiveness, immunogenicity or safety of Flucelvax Quad, or the safety of Flucelvax
2. The study is in a language other than English or French
3. The study is a non-human or *in vitro* study



4. The article is not a primary research study
5. The article is an editorial, opinion, commentary or news report
6. The article is an economic study, clinical practice guidelines, consensus conference or health technology assessment report
7. The article was a doctoral dissertation, master’s thesis or conference summary

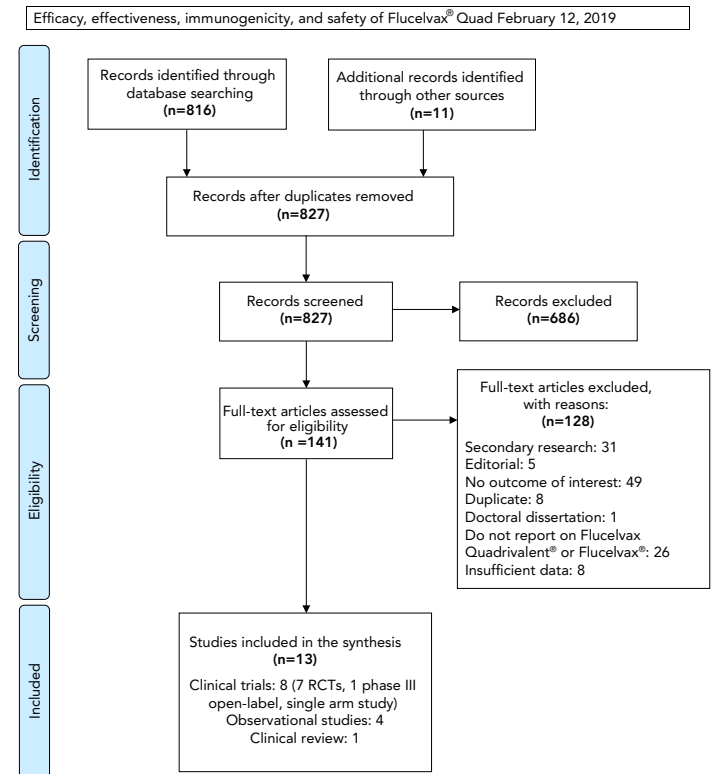
Flucelvax Quad has overlapping composition with Flucelvax, which is a trivalent cell culture-based influenza vaccine (IIV3-cc) produced using the same MDCK manufacturing platform (12,13). Therefore, studies that assessed the safety of Flucelvax were also included in this literature review *post hoc* to supplement the evidence base for the safety outcome. Specialty trivalent vaccines (i.e. high-dose trivalent inactivated influenza vaccine [IIV3-HD] and adjuvanted trivalent inactivated influenza vaccine [IIV3-adj]) were also added as comparator vaccines *post hoc*, since these comparisons would originally have been excluded as there is currently no comparable quadrivalent formulation of these vaccines.

Data from included studies were extracted into evidence tables using a piloted data abstraction template. The quality (internal validity) of included studies was assessed using criteria outlined by Harris *et al.* (14). Data extraction and quality assessment were completed by one reviewer and verified by a second reviewer. Results from included studies were synthesized narratively and analyzed according to NACI evidence-based process (15) to develop a new recommendation. Following thorough review of the evidence, NACI approved the recommendation.

## Results

The systematic review retrieved 827 unique articles, of which thirteen were retained for data extraction and analysis. Four studies reported on the effectiveness of IIV4-cc. Two peer-reviewed studies (one in adults and one in children) investigated the immunogenicity and safety of IIV4-cc. No studies that assessed the immunogenicity of Flucelvax Quad compared to egg-based IIV (trivalent or quadrivalent) were identified. One clinical review of cases and six peer-reviewed randomized controlled trials (RCTs) (four in adults and two in children) provided evidence for the safety of IIV3-cc. No efficacy studies for IIV4-cc were identified and studies evaluating the efficacy of IIV3-cc were beyond the scope of the systematic review. A flow diagram of the study selection process is presented in **Figure 1**. Key study characteristics are summarized in **Tables 1** and **2**.

**Figure 1: PRISMA flow diagram of the study selection process for the systematic review on the efficacy, effectiveness, immunogenicity and safety of Flucelvax Quad**



**Table 1: Characteristics of IIV4-cc studies included in the systematic review**

Study	Design (vaccine)	Study population	Outcomes
DeMarcus <i>et al.</i> (2019)	<ul style="list-style-type: none"> <li>• Test-negative case-control</li> <li>• 2017–2018 influenza season</li> <li>• (IIV4-cc versus egg-based IIV4)</li> </ul>	<ul style="list-style-type: none"> <li>• US DOD healthcare beneficiaries six months–94 years of age</li> <li>• 1,757 cases (laboratory-confirmed):                             <ul style="list-style-type: none"> <li>- 531 vaccinated; IIV4-cc (n=192), egg-based IIV4 (n=339)</li> </ul> </li> <li>• 2,280 controls:                             <ul style="list-style-type: none"> <li>- 977 vaccinated; IIV4-cc (n=314), egg-based IIV4 (n=663)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• VE against laboratory-confirmed influenza</li> <li>• OR for individuals vaccinated with cell-derived vaccine compared to egg-derived vaccine</li> </ul>

**Table 1: Characteristics of IIV4-cc studies included in the systematic review (continued)**

Study	Design (vaccine)	Study population	Outcomes
Izurieta et al. (2018)	<ul style="list-style-type: none"> <li>Retrospective cohort</li> <li>2017–2018 influenza season</li> <li>(IIV4-cc vs egg-based IIV4-SD, egg-based IIV3-SD, IIV3-adj, IIV3-HD)</li> </ul>	<ul style="list-style-type: none"> <li>Medicare beneficiaries 65 years of age and older</li> <li>- IIV4-cc (n=653,099)</li> <li>- Egg-based IIV4-SD (n=1,844,745)</li> <li>- Egg-based IIV3-SD (n=8,449,508)</li> <li>- IIV3-adj: (n=1,465,747)</li> <li>- IIV3-HD (n=1,007,082)</li> </ul>	<ul style="list-style-type: none"> <li>rVE for influenza-related health care interactions</li> </ul>
Boikos et al. (2018) NCT 01992094	<ul style="list-style-type: none"> <li>Retrospective cohort</li> <li>(IIV4-cc vs egg-based IIV4)</li> <li>2017–2018 influenza season</li> </ul>	<ul style="list-style-type: none"> <li>EMR of US patients four years of age or older</li> <li>- IIV4-cc (n=92,192)</li> <li>- Egg-based IIV4 (n=1,255,983)</li> </ul>	<ul style="list-style-type: none"> <li>Propensity-score matched rVE against ILI</li> </ul>
Klein et al. (2018)	<ul style="list-style-type: none"> <li>Retrospective cohort</li> <li>2017–2018 influenza season</li> <li>(IIV4-cc vs egg-based IIV)</li> </ul>	<ul style="list-style-type: none"> <li>Kaiser Permanente members 4–64 years of age</li> <li>- IIV4-cc (n=932,874)</li> <li>- Egg-based IIV (n=84,440)</li> </ul>	<ul style="list-style-type: none"> <li>rVE against laboratory-confirmed influenza A(H3N2)</li> <li>rVE against all laboratory-confirmed influenza</li> </ul>
Bart et al. (2016)	<ul style="list-style-type: none"> <li>RCT</li> <li>2013–2014 influenza season</li> <li>(IIV4-cc vs IIV3-cc)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy adults 18 years of age and older</li> <li>- IIV4-cc (n=1,335)</li> <li>- IIV3-cc, B/Yam (n=676)</li> <li>- IIV3-cc, B/Vic (n=669)</li> </ul>	<ul style="list-style-type: none"> <li>GMT ratio 22 days post-vaccination</li> <li>Seroconversion rate three weeks (day 22) post-vaccination</li> <li>HI antibody response</li> <li>Seroprotection rate</li> <li>Solicited AEs within seven days of vaccination</li> <li>Unsolicited AEs (day 1–22 post-vaccination)</li> </ul>
Hartvickson et al. (2015) NCT01992107	<ul style="list-style-type: none"> <li>RCT</li> <li>2013–2014 influenza season</li> <li>(IIV4-cc vs IIV3-cc)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy children 4–18 years of age; stratified into two age cohorts: 4–9 years of age and 9–18 years of age</li> <li>- IIV4-cc (n=1,159)</li> <li>- IIV3-cc, B/Yam (n=593)</li> <li>- IIV3-cc, B/Vic (n=581)</li> </ul>	<ul style="list-style-type: none"> <li>GMT ratio 22 days post-vaccination</li> <li>Seroconversion rate three weeks (day 22) post-vaccination with last dose</li> <li>Seroprotection rate</li> <li>Solicited AEs within seven days of vaccination</li> <li>Unsolicited AEs (within 22 days of vaccination)</li> </ul>

Abbreviations: AE, adverse event; EMR, Electronic medical record; GMT, geometric mean titre; HI, hemagglutination inhibition; IIV, inactivated influenza vaccine; IIV3, trivalent inactivated influenza vaccine; IIV3-adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-cc, cell-culture based trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccines; IIV4-cc, cell-culture based quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; ILI, influenza-like illness; NCT, National clinical trial number; OR, odds ratio; RCT, randomized controlled trial; rVE, relative vaccine effectiveness; US DOD, United States Department of Defense; VE, vaccine effectiveness

**Table 2: Characteristics of IIV3-cc studies included in the systematic review**

Study	Design (vaccine)	Study population	Outcomes
Ambrozaitis et al. (2009)	<ul style="list-style-type: none"> <li>RCT</li> <li>2005–2006 influenza season</li> <li>(IIV3-cc versus egg-based IIV3)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy adults 18–60 years of age</li> <li>IIV3-cc (n=1,028)</li> <li>Egg-based IIV3 (n=171)</li> </ul>	<ul style="list-style-type: none"> <li>AEs within seven days of vaccination</li> </ul>
Szymczakiewicz-Multanowska et al. (2009) NCT00492063	<ul style="list-style-type: none"> <li>Phase III, observer blind RCT</li> <li>2004–2005 influenza season</li> <li>(IIV3-cc vs egg-based IIV3)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy adults 18 years of age and older</li> <li>IIV3-cc: <ul style="list-style-type: none"> <li>- 18–60 years of age (n=652)</li> <li>- 61 years of age and older (n=678)</li> </ul> </li> <li>Egg-based IIV3: <ul style="list-style-type: none"> <li>- 18–60 years of age (n=648)</li> <li>- 61 years of age and older (n=676)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>AEs within seven days of vaccination</li> </ul>
Nolan et al. 2016	<ul style="list-style-type: none"> <li>Phase III, observer blind RCT</li> <li>2013–2014 influenza season</li> <li>(IIV3-cc vs egg-based IIV3)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy children and adolescents 4–17 years of age</li> <li>IIV3-cc (n=1,372)</li> <li>Egg-based IIV3 (n=683)</li> </ul>	<ul style="list-style-type: none"> <li>AEs within seven days of vaccination</li> </ul>
Vesikari et al. (2012)	<ul style="list-style-type: none"> <li>Phase II/III, observer-blind RCT</li> <li>October 2007–July 2008</li> <li>(IIV3-cc vs egg-based IIV3)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy children and adolescents 3–17 years of age</li> <li>IIV3-cc two doses 3–8 years of age (n=1,599)</li> <li>IIV3-cc single dose 9–17 years of age (n=652)</li> <li>Egg-based IIV3 3–8 years of age (n=1,013)</li> <li>Egg-based IIV3 9–17 years of age (n=316)</li> </ul>	<ul style="list-style-type: none"> <li>AEs within seven days of vaccination</li> </ul>
Frey et al. (2010) NCT00630331	<ul style="list-style-type: none"> <li>Observer-blind RCT</li> <li>2007–2008 influenza season</li> <li>(IIV3-cc vs egg-based IIV3)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy adults 18–49 years of age</li> <li>IIV3-cc (n=3,813)</li> <li>Egg-based IIV3 (n=3,669)</li> <li>Placebo (n=3,894)</li> </ul>	<ul style="list-style-type: none"> <li>AEs within seven days of vaccination</li> </ul>



**Table 2: Characteristics of IIV3-cc studies included in the systematic review (continued)**

Study	Design (vaccine)	Study population	Outcomes
Loebermann et al. (2019) NCT01880697	<ul style="list-style-type: none"> <li>Phase III open-label, single-arm, study</li> <li>2013–2014 influenza season</li> <li>(IIV3-cc)</li> </ul>	<ul style="list-style-type: none"> <li>Healthy adults</li> <li>IIV3-cc:               <ul style="list-style-type: none"> <li>18–60 years age (n=63)</li> <li>61 years age and older (n=63)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>AEs following vaccination</li> </ul>
Moro et al. (2015)	<ul style="list-style-type: none"> <li>Clinical review of cases identified through VAERS</li> <li>2013–2014, 2014–2015 influenza seasons</li> <li>(IIV3-cc)</li> </ul>	<ul style="list-style-type: none"> <li>Persons vaccinated with IIV3-cc during July 1, 2013 through March 31, 2015 (reports received by April 30, 2015); excluding non-US reports</li> <li>Total reports reviewed: n=629</li> <li>Persons vaccinated with IIV3-cc July 1, 2013–March 31, 2015 (reports received by April 30, 2015); excluding non-US reports</li> <li>Reports with an AE:               <ul style="list-style-type: none"> <li>n=309</li> <li>during 2013–2014 influenza season (n=389)</li> <li>during 2014–2015 influenza season (n=240)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>AEs following vaccination</li> </ul>

Abbreviations: AE, adverse event; IIV3, trivalent inactivated influenza vaccine; IIV3-cc, cell-culture based trivalent inactivated influenza vaccine; NCT, National clinical trial number; RCT, randomized controlled trial; US, United States; VAERS, Vaccine Adverse Event Reporting System

## Vaccine efficacy and effectiveness

Four observational studies, two peer-reviewed and two not peer-reviewed, were identified that assessed the vaccine effectiveness of IIV4-cc compared to egg-based IIV against laboratory-confirmed influenza infection during the 2017–2018 influenza season in the US (16–19). Of these four studies, two were of good quality (17,18) according to the criteria outlined by Harris et al. (14), while the quality of the other two studies (16,19) could not be assessed because they were published as conference abstracts or posters. There were some data indicating that IIV4-cc may offer improved protection against influenza compared with conventional egg-based IIV4 or IIV3, particularly

against A(H3N2) virus infection. The IIV4-cc may also be more effective than egg-based trivalent or quadrivalent influenza vaccines against non-laboratory confirmed influenza-related outcomes, including influenza-related health care interactions and influenza-like illness, but there was insufficient evidence for laboratory-confirmed outcomes. Although some data suggests 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.

## Immunogenicity

Two peer-reviewed studies (20,21) that reported on the immunogenicity and safety of Flucelvax Quadrivalent compared with different IIV3-cc formulations were identified in this review; one study by Bart et al. (20) was conducted with adult subjects 18 years of age and older, while the other study by Hartvickson et al. (21) focused on pediatric subjects four to 17 years of age. The immunogenicity outcomes assessed by these studies included geometric mean-fold rise in haemagglutination assay (HA) titres (i.e. ratio of post to pre-vaccination geometric mean titre), seroprotection rate (i.e. proportion of participants with HA titres of at least 40 post-vaccination) and seroconversion rate (i.e. proportion of participants with at least a four-fold increase in HA titres post-vaccination, HA titre increase from less than 10 pre-vaccination to at least 40 post-vaccination, or both). In both studies, IIV4-cc demonstrated non-inferiority, based on geometric mean titre (GMT) ratio and seroconversion rates, and met the threshold for seroprotection for all influenza strains contained in the IIV3-cc vaccines.

The immunogenicity of Flucelvax Quad is further supported by evidence from the clinical development program for Flucelvax that has been licensed in the US, but for which licensure has never been sought in Canada. Flucelvax has demonstrated non-inferiority to standard egg-based IIV3 comparators for hemagglutination inhibition (HI) antibody responses overall to any strain in adults 18 years of age and older and for A(H1N1) and B strains specifically, but not A(H3N2), for persons four to 17 years of age, based on post-vaccination GMT ratios and seroconversion rates (22–25). Notably, IIV3-cc was manufactured using egg-derived CVVs prior to the implementation of manufacturing methods using CVVs solely derived from MDCK cells.

## Safety

Two peer-reviewed studies assessed the safety of Flucelvax Quadrivalent (IIV4-cc) compared with different IIV3-cc formulations; one focused on healthy adults (20) and the other on healthy children four years of age and older (21). The safety outcomes assessed included solicited local and systemic adverse events (AE) from day 1–7 post-vaccination, serious adverse events (SAE) through six months after the last vaccination, and unsolicited AEs from day 1–23 post-vaccination. The reported



solicited local and systemic AE for both adults and children were generally mild to moderate in intensity, self-limited, and did not precipitate sequelae. Serious adverse events were rare and similar in frequency between the quadrivalent and trivalent formulations of the cell culture-based vaccines being compared. No studies that assessed the safety of IIV4-cc compared with egg-based IIV (trivalent or quadrivalent) were identified in this review.

Flucelvax Quadrivalent has been licensed in the US for use in adults and children four years or older in since 2016. Since authorization, no safety signals have been identified through routine pharmacovigilance. One clinical review of cases (26) and six peer-reviewed RCTs (1,27–31) (four in adults and two in children) that reported on the safety of IIV3-cc were included in the review to supplement the evidence base for the safety outcome. The evidence on safety was consistent across studies and showed that there was no significant difference in adults and children four years of age and older who had received the IIV3-cc and egg-based IIV3. Overall, Flucelvax was safe and well tolerated, with local and systemic solicited reactions as well as unsolicited AE and SAE comparable to those typically observed with other injectable egg-derived IIV3. The IIV3-cc also has an established record of safety, and no new safety signals have been identified through routine pharmacovigilance in the US or Europe where the vaccine has been licensed (22,23,25).

## Discussion

Flucelvax Quad is considered effective, immunogenic and safe in adults and children nine years of age and older, and has a comparable immunogenicity and safety profile to 1) egg-based influenza vaccines already licensed in Canada and 2) Flucelvax, which is a trivalent cell culture-based influenza vaccine that has been licensed in the US, but for which licensure has never been sought in Canada. The cell culture-based Flucelvax Quad can also provide broader protection against influenza B viruses when compared with trivalent influenza vaccines. There is a theoretical concern that inactivated influenza vaccines produced in canine kidney cells (MDCK 33016-PF) may cause adverse reactions in individuals with dog allergy. However, evidence from *in vitro* studies on the allergenicity of MDCK cell-based vaccines in individuals with documented allergies associated with dogs, as well as IIV-cc clinical trials and post-market safety surveillance, does not suggest that there is an elevated risk of hypersensitivity reactions as compared with egg-based influenza vaccines (32,33).

Implementation of cell culture-based influenza vaccine technologies and other alternatives to egg-based methods can also enable diversification of vaccine manufacturing platforms to overcome influenza vaccine supply vulnerabilities and improve vaccine-production capacity. Nevertheless, adaptation in cell culture-based influenza vaccines needs to be further investigated given the potential for mutations in the genetic segments of hemagglutinin and neuraminidase surface proteins resulting

from serial passaging in MDCK cells (34,35). A more robust, comprehensive and consistent body of evidence, including data on comorbidities, pregnant women, health status, and other potential confounders (36), also needed to evaluate the relative effectiveness and safety of Flucelvax Quad compared with other injectable influenza vaccines. Therefore, ongoing monitoring of vaccine effectiveness, immunogenicity and safety will be important to compare prior and future seasons, across influenza subtypes and overall vaccine effectiveness for each vaccine type.

## Limitations

There are limited peer-reviewed studies currently available on the effectiveness, immunogenicity and safety of IIV4-cc manufactured using fully cell-derived CVVs. All studies that assessed effectiveness were conducted in the US during the same season (2017–2018), which was influenza A(H3N2)-dominant. As influenza seasons can vary widely from year to year, interpretation of the data from these observational studies is limited and further evidence on effectiveness gathered during influenza seasons with different circulating viruses is needed before a conclusion on the relative effectiveness can be made. Two of the observational studies (16,18) evaluating vaccine effectiveness utilized real-world primary care data from the electronic medical records of individual patients. The use of electronic medical record datasets for influenza vaccine effectiveness estimation has not yet been validated and the potential sources of bias and confounding still need to be further investigated. Furthermore, the clinical significance and directness of the evidence provided by influenza-related outcomes, which are surrogate measures of influenza activity, remain uncertain.

## NACI recommendation for individual level decision-making

The following recommendation for Flucelvax Quad supplements NACI's overarching recommendation for influenza vaccination, which is available in the NACI Seasonal Influenza Vaccine Statement. The overarching NACI recommendation for influenza vaccination is that an age appropriate influenza vaccine should be offered annually to anyone six months of age and older (Strong NACI Recommendation), noting product-specific contraindications.

1. **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)**



The detailed findings of the literature review, and rationale and relevant considerations for this recommendation can be found in the NACI *Supplemental Statement – Mammalian Cell-Culture Based Influenza Vaccines* (37).

## Conclusion

There is fair evidence that Flucelvax Quad is effective, safe and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults and children nine years of age and older. NACI recommends that Flucelvax Quad may be considered among the IIV4 offered to adults and children nine years of age and older. NACI will continue to monitor the evidence related to cell-culture based influenza vaccines and will update this supplemental statement as needed and as data on Flucelvax Quad from several different influenza seasons accumulates.

## Authors' statement

AS — Writing, original draft, review, editing

IG — Review, editing

RH — Review, editing

The National Advisory Committee on Immunization (NACI) *Canadian Immunization Guide Chapter and Statement on Seasonal Influenza Vaccine 2020–2021: Supplemental Statement – Mammalian Cell-Culture Based Influenza Vaccines* was prepared by A Sinilaite, J Przepiorkowski, K Young, I Gemmill, and R Harrison on behalf of the NACI Influenza Working Group and was approved by NACI.

## Competing interests

None.

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