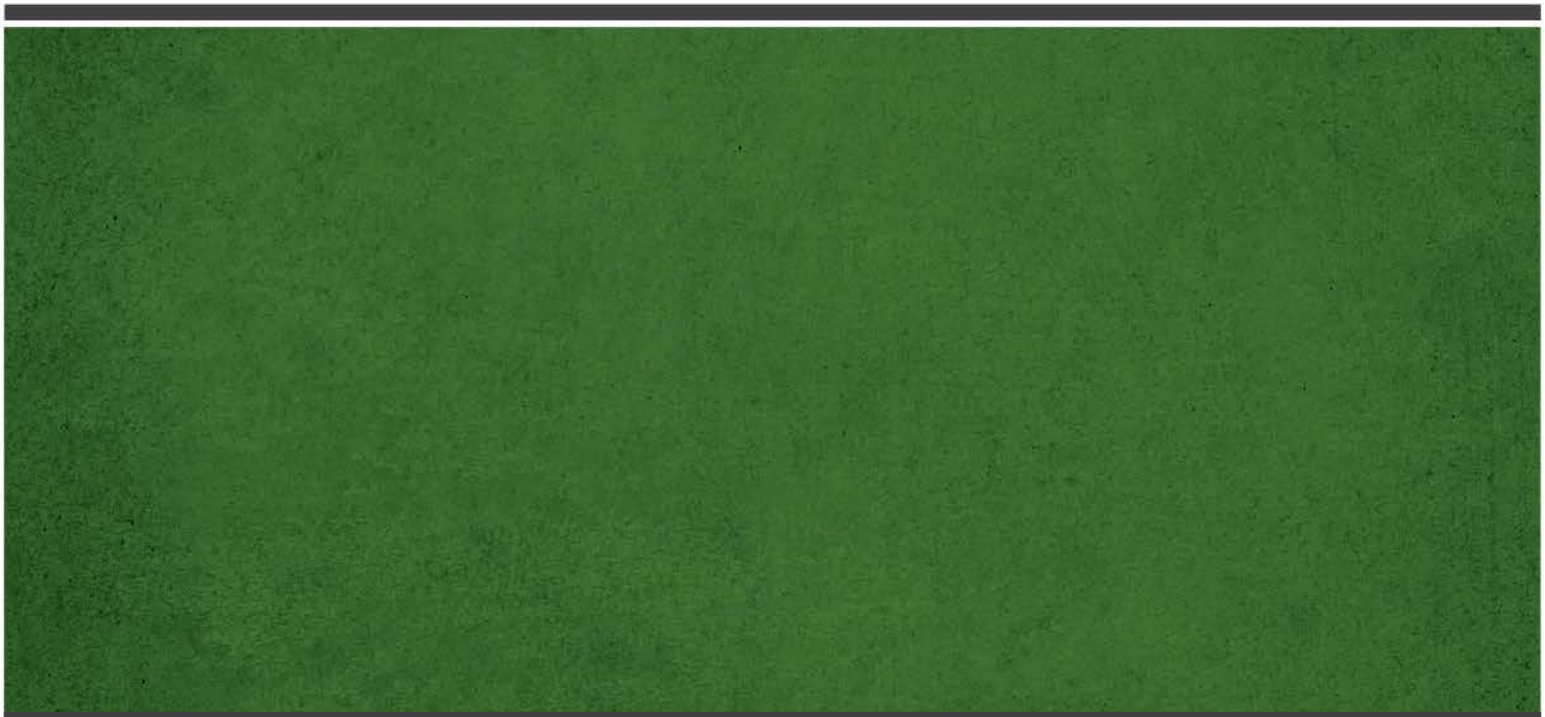
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Updated Guidance on Influenza Vaccination During Pregnancy



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PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing, and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: ethics, equity, feasibility, acceptability (EEFA), and economics. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of the statement for details.

1. What

Seasonal influenza infection is a respiratory illness that can lead to serious complications and adverse outcomes, particularly for pregnant individuals, the developing fetus, and infants under 6 months old. Influenza vaccination is safe and the best way to prevent infection in both pregnant people and infants under 6 months old. Pregnant individuals are prioritized to receive influenza vaccines because of the increased risks of severe disease during pregnancy; despite this, influenza vaccination uptake among this group remains suboptimal.

The following recommendations for influenza vaccination in pregnancy supplement NACI's overarching recommendations for influenza vaccination, which are available in the NACI Seasonal Influenza Vaccine Statement. NACI recommends that individuals at any stage of pregnancy should receive an age-appropriate inactivated unadjuvanted (IIV) or recombinant influenza vaccine (RIV) each influenza season.

2. Who

This supplemental statement provides an evidence summary on the safety and vaccine effectiveness (VE) of influenza vaccination in pregnant individuals, and the benefits and risks to the developing fetus and infants under 6 months of age.

3. How

IIV or RIV should be offered annually, at any gestational age, during pregnancy. Influenza vaccination may be given at the same time as, or at any time before or after administration of another vaccine, including the COVID-19 or pertussis vaccine.

4. Why

Pregnant people, their fetuses, and infants are at high risk of complications from influenza; therefore, annual influenza vaccination during pregnancy is strongly recommended. Influenza vaccination during pregnancy has consistently been shown to be safe and is supported by numerous studies, moreover vaccination has been shown to reduce the morbidity and mortality associated with influenza infection. Additionally, since influenza-related outcomes experienced during pregnancy can negatively impact the development of the fetus, vaccination of the pregnant person helps protect the fetus. Furthermore, passive transfer of antibodies from vaccination during pregnancy protects newborns during their first months of life when they are at high risk of complications from influenza infection, and too young to be immunized. Overall, the evidence supports the safety and VEs of influenza vaccines during pregnancy.

I. INTRODUCTION

I.1 Background on influenza vaccines, immunization programs and recommendations during pregnancy in Canada

Prior to the COVID-19 pandemic, influenza viruses caused approximately 40,000 laboratory-confirmed influenza (LCI) cases, 12,200 hospitalizations, and 3,500 deaths among Canadians each year [1-3]. As such, NACI recommends that influenza vaccine should be offered annually to anyone 6 months of age and older who does not have a contraindication to the vaccine. NACI has also identified groups at higher risk of influenza complications for whom influenza vaccination is particularly recommended ***(Strong NACI recommendation).***

NACI has identified pregnant individuals as one of the high-risk groups for whom influenza immunization is particularly important. Because of pregnancy-related changes in anatomy and the immune and cardiovascular systems, pregnant individuals are at higher risk for severe influenza disease and related complications such as pneumonia, hospitalization, and death compared to non-pregnant individuals [4-6]. Influenza infection during pregnancy not only affects pregnant persons, but can also impact the developing fetus, and increases the risk of late-stage pregnancy loss, still birth, low birth weight and pre-term birth [6, 7]. Therefore, immunizing pregnant persons against influenza is strongly recommended to protect both them and their infants from severe disease, especially as infants under 6 months of age are not eligible for influenza vaccination.

The NACI recommendations for the use of influenza vaccines in pregnancy and breastfeeding have evolved over time. Prior to 2007, NACI encouraged all pregnant people to be vaccinated against influenza but did not identify pregnant people without comorbidities as a priority group for vaccination programs. In 2007, NACI revised its recommendation to identify all pregnant individuals as a group for whom influenza vaccine is particularly recommended by nature of being at high-risk of influenza-related complications. NACI now also highlights that influenza vaccination in pregnancy protects both pregnant individuals and their newborn infants with passive immunity via transplacentally-transferred antibodies from the pregnant person up to the time infants can receive the vaccine themselves.

Despite pregnant people being prioritized to receive influenza vaccines because of the increased risks of severe disease, vaccine uptake remains lower compared to the non-pregnant population. Further, a disproportionate burden of disease and low uptake is observed among populations who are pregnant and racialized, Indigenous, younger, and/or have lower household income [8-11].

More literature continues to be published on the safety, efficacy, and effectiveness of influenza vaccines in pregnancy. The need for this NACI Supplemental Statement on the use of influenza vaccines during pregnancy was triggered by a study identifying a potential risk of increased early spontaneous abortion in pregnant people who received influenza vaccines in 2010 and 2011 [12]. Since then, several studies have been published finding no association of influenza vaccines administered during pregnancy and adverse outcomes in pregnant persons or infants [13-16].

NACI has taken this opportunity to review the safety, efficacy, and effectiveness of influenza vaccine in pregnancy. Moreover, this statement aims to synthesize the key information and evidence to support provincial and territorial vaccine programs and primary care providers in offering influenza vaccine to pregnant individuals.

The beneficial effects of immunization during pregnancy for the fetus as well as the newborn infant have been well documented. Vaccination during pregnancy has consistently been shown to be safe and protects the pregnant individual from vaccine-preventable diseases that may otherwise be acquired and transmitted to the fetus or infant. In addition, protective concentrations of antibodies are transferred to the fetus transplacentally, which usually results in infant protection from infection in the first few months of life. For information on the benefits and safety of recommended vaccines during pregnancy and breastfeeding, refer to the Immunization in pregnancy and breastfeeding chapter in the Canadian Immunization Guide (CIG).

I.2 Guidance objective

The following advisory committee statement on influenza vaccination in pregnancy supplements NACI's overarching recommendations for influenza vaccination, which are available in the NACI Seasonal Influenza Vaccine Statement. The objective of this supplemental statement is to provide updated guidance on the use of influenza vaccination during pregnancy. The statement describes the disproportionate risk of morbidity and mortality for pregnant individuals and infants under 6 months old who acquire influenza compared to the general population; reviews the available evidence on the efficacy, effectiveness, and safety of influenza vaccination during pregnancy; and explores the EEFA considerations of immunizing pregnant people against influenza. Based on this body of evidence, the supplemental statement reaffirms the safety and importance of influenza vaccination during pregnancy.

Breastfeeding

It is recognized that pregnant and breastfeeding individuals are closely overlapping populations; however, there are differences in the considerations of vaccination for each. The purpose of this supplemental statement is to examine influenza vaccination in pregnancy specifically, given an identified possible concern regarding its safety. Therefore, this supplemental statement does not examine the safety and effectiveness of influenza vaccination during breastfeeding.

As stated in the NACI Seasonal Influenza Vaccine Statement, annual influenza vaccination is recommended during breastfeeding, and either non-live influenza vaccines or live attenuated influenza vaccine (LAIV) can be administered to breastfeeding individuals. There have been no identified safety signals for influenza vaccination in breastfeeding, and no hypothesized biological mechanism for a safety issue with currently authorized products. For more information on this topic, please see the aforementioned Statement and CIG chapter on Immunization in pregnancy and breastfeeding.

A note on language

NACI recognizes that not all people giving birth or breastfeeding will identify as women or mothers. Much of the research available currently refers only to “women” when discussing pregnancy. When citing research, NACI refers to the language used in the study. In these cases, “woman” refers to someone who was assigned female at birth and “maternal” is used to identify the person who is pregnant or postpartum. For the purposes of this statement, the terms "woman", "women", and "maternal" should be considered to also apply to those individuals who do not specifically identify as female gender but are the parent gestating the fetus or breastfeeding/chestfeeding the infant.

II. METHODS

In brief, the broad stages in the preparation of a NACI statement are:

1. Knowledge synthesis: retrieval and summary of literature, assessment of the quality of the evidence (summarized in Table 1: Summary of Evidence).
2. Synthesis of the body of evidence: benefits (efficacy and effectiveness) and potential harms (safety), considering the quality of the synthesized evidence and, where applicable, the magnitude of effects observed across the studies.
3. Use of a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to EEFA are systematically assessed and integrated into the guidance [17]. Completion of health economic analyses as needed.
4. Use of the evidence to inform recommendations.

Further information on NACI's process and procedures is available elsewhere.

To meet the objectives of this statement, a *de novo* systematic review (SR) was conducted to gather evidence to inform NACI's recommendations regarding the use of influenza vaccines during pregnancy. The methodology was specified *a priori* in a written protocol [18]. The review protocol and knowledge synthesis were developed and performed in collaboration with the Methods and Applications Group for Indirect Comparisons (MAGIC) through the Drug Safety and Effectiveness Network (DSEN) and supervised by the NACI Influenza Working Group (IWG). An update to the literature search was completed by the NACI Secretariat in conjunction with a librarian from the Health Library of Health Canada and PHAC. A health economic analysis was not conducted as it was not deemed necessary for this statement. The evidence and proposed recommendations were presented to NACI for deliberation on April 27, 2023, and approved following a thorough review of the evidence. Relevant considerations, rationale for specific decisions, and knowledge gaps are described in the following sections.

For a comprehensive description of the review methods, including details on the study eligibility, literature search, study selection, data collection and statistical methods, please refer to Wolfe et al. (2020) [18]. Methods related to the review update completed by the NACI Secretariat are reported in Appendix A.

The policy question addressed in this statement is: **Should pregnancy (regardless of gestational age) continue to be listed as one of the risk categories for priority influenza vaccination?**

To meet the objective of this statement, other informal literature reviews were conducted as needed to gather data and information including:

- Epidemiology and estimated burden of influenza illness among pregnant persons and infants under 6 months of age;

- An environmental scan of recommendations and considerations for use of influenza vaccines during pregnancy in Canadian provinces and territories and in other high-income countries.

To develop comprehensive and appropriate immunization program recommendations, NACI considers several factors. In addition to critically appraising evidence on burden of disease and vaccine characteristics such as safety, efficacy, immunogenicity and effectiveness, NACI applies the EEFA framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely and transparent decision-making [19]. For details on the development and application of NACI's EEFA Framework and aforementioned evidence-informed tools, please see Ismail et al. (2020) [19].

III. EPIDEMIOLOGY

III.1 Estimated burden of influenza among pregnant persons

Pregnant individuals are more susceptible to severe influenza illness throughout pregnancy, notably in the third trimester [20-24]. A 2019 meta-analysis (MA) on seasonal and pandemic (H1N1) influenza found that pregnant persons had a 7-times higher risk of influenza-associated hospital admission compared to non-pregnant persons (odds ratio [OR]=6.80; 95% confidence interval [CI]: 6.02-7.68), but were not at higher risk for intensive care unit (ICU) admission or death [22]. During the 2009 H1N1 pandemic however, a SR demonstrated that pregnant persons had a greater risk of influenza-related hospitalization, ICU admission, and death compared to non-pregnant persons [25]. Particularly, the median relative risk of influenza infection was 6.8 (range 3.5-25.3) compared to the general population.

III.2 Estimated impact of influenza on perinatal outcomes

Influenza infection during pregnancy can result in serious perinatal outcomes. A 2021 meta-analysis of worldwide studies on seasonal and pandemic (H1N1) influenza reported that pregnant individuals had a 3-times higher risk of stillbirth following influenza infection (risk ratio [RR]=3.62; 95% CI: 1.60 to 8.20) [26]. Studies from Australia, India, Peru, and Thailand also discovered a significant link between seasonal influenza infection during pregnancy to lower birth weight and late pregnancy loss [6, 27]. Moreover, a 2017 SR reported limited, mixed evidence when evaluating the risk of adverse birth outcomes, including preterm birth, small-for-gestational-age (SGA) birth, or fetal death, in individuals with clinical influenza disease or LCI infection during pregnancy compared to those without influenza [28]. Although a small subgroup of higher-quality studies reported an association between pandemic H1N1 influenza (pH1N1) disease and preterm birth (with RRs ranging from 2.4 to 4.0 for severe disease) and fetal death (RR of 1.9 for mild-to-moderate disease and 4.2 for severe disease), no firm conclusions about the magnitude of the association can be drawn at this time based on these limited data.

III.3 Estimated burden of influenza among infants under 6 months of age

Young infants are particularly vulnerable to influenza infection and its complications due to their underdeveloped immune systems and ineligibility for the influenza vaccine. Influenza is a leading cause of respiratory infection among children under age 1 year and causes approximately 280,000 respiratory hospitalizations globally in those under 6 months old each year (95% CI: 150,000 to 344,000) [7, 29-31]. In 2018, hospital admissions and in-hospital deaths due to seasonal influenza in children under 5 years of age occurred disproportionately in infants under 6 months old (23% and 36%, respectively) and predominantly in low and lower-middle-income countries [32]. In Canada, a national active surveillance study of pediatric influenza admissions revealed that infants under 6 months old accounted for 13.5% of children under 16 years of age admitted for influenza during 2010-2011 to 2020-2021, emphasizing the significant

burden of influenza and its associated complications for this age group [33]. Furthermore US surveillance data from 2004-2012 reported that infants under 3 months of age were 40% more likely while those aged 3-6 months were 45% more likely to be admitted to the ICU with LCI compared to infants aged 6-12 months (OR=1.40; 95% CI: 1.04 to 1.88 and OR=1.45; 95% CI: 1.03 to 2.04, respectively) [29]. The influenza-associated mortality rate was estimated at 0.66 (95% CI: 0.53 to 0.82) [34]. During the 2009 H1N1 pandemic, a U.S. study reported a LCI hospitalization rate of 20.2 per 10,000 infants under 6 months of age [35].

III.4 Influenza vaccination coverage among pregnant persons in Canada

In Canada, influenza vaccination coverage in pregnancy increased from 45.0% in 2019 to 52.7% in 2021 [36]. However, coverage varied by province/territory; in 2021, Nova Scotia had the highest vaccination rate (82.5%) and Quebec had the lowest (44.2%). Overall, vaccination coverage increased in all jurisdictions from 2019 to 2021, except Saskatchewan (64.9% to 64.8%, respectively) and the Northwest Territories (84.8% to 71.7%, respectively). Vaccination coverage also varied by Indigenous status and income. The gap in influenza vaccination coverage between Indigenous pregnant people and non-Indigenous pregnant people increased in 2021 (vaccination coverage of 28% vs. 54% respectively) compared with 2019 (vaccination coverage of 35% vs. 46% respectively) [36]. As well, those in lower income groups (household income under $80,000) had lower vaccination rates against influenza relative to those in the highest household income group [36].

IV. VACCINE

IV.1 Concurrent administration with other vaccines

Influenza vaccines may be administered concurrently with (i.e., same day), or at any time before or after, other vaccines recommended during pregnancy. Current evidence suggests that administering recommended vaccines concurrently during pregnancy is safe, despite the potential increase in local and systemic adverse reactions, including fever. There is no evidence to support adverse pregnancy sequelae from fever related to vaccine reactogenicity. A cohort study conducted in Australia involving 1,851 participants who received both IIV3 and tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis (Tdap) vaccines concurrently during pregnancy found a low incidence of adverse events (AEs), providing support for the safety of concurrent vaccine administration during pregnancy [37]. Other studies have similarly reported no significant safety concerns with concurrent administration of these vaccines during pregnancy [38, 39].

IV.2 Efficacy and effectiveness

The DSEN SR assessed the effect of seasonal influenza vaccination during pregnancy against influenza-related infection and hospitalization in pregnant persons and/or their infants using findings from 4 randomized controlled trials (RCTs) [40-43] and 2 observational studies [44, 45]. Additional observational studies (n=6) were identified from the updated literature search reporting data on influenza VE in pregnant persons and/or their infants up to 6 months of age [46-51].

IV.2.1 Benefits to the pregnant person: Vaccine efficacy/effectiveness outcomes

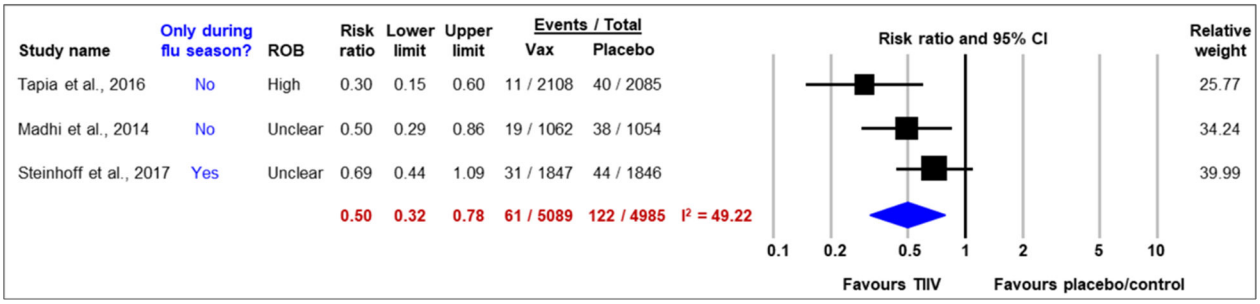
Summary of study characteristics

Overall, 4 studies reported data on LCI and 3 reported data on hospitalization due to LCI infection during pregnancy or up to 6 months post-partum. Among those, 3 RCTs compared the efficacy of seasonal influenza vaccination during pregnancy to placebo (n=2) [40, 41] or active comparator (n=1; meningococcal quadrivalent vaccine, Menactra®, Sanofi) [42] against LCI from enrollment to 6 months post-partum. In the 3 RCTs, the occurrence of LCI among 5,089 people receiving IIV was compared to 4,985 people randomized to the placebo or active comparator group. One (1) prospective cohort study identified from the updated literature search evaluated the effectiveness of seasonal IIV4 compared to no influenza vaccination during pregnancy against LCI [46]. One (1) study identified from the DSEN SR that used a test-negative study design evaluated the VE of seasonal influenza vaccination amongst pregnant persons hospitalized for acute respiratory or febrile illness against LCI infection [44]. One (1) prospective cohort study, 1 prospective case-control study and 1 test-negative study design identified from the updated literature search evaluated the effectiveness of seasonal influenza vaccination during pregnancy on LCI hospitalization in pregnant persons [47, 48, 52].

Summary of vaccine efficacy/effectiveness

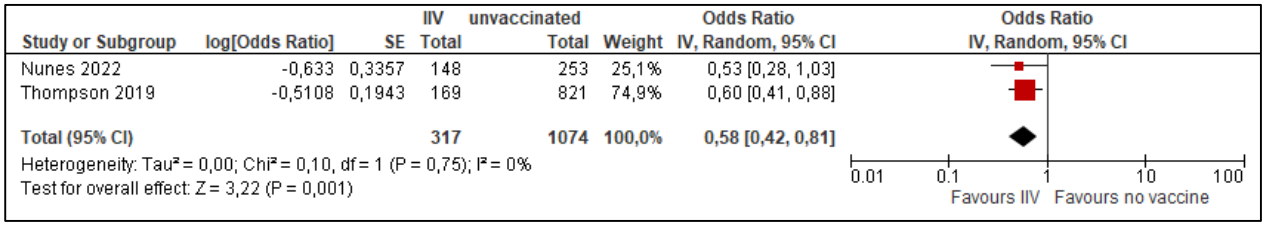
A MA of the 3 RCTs suggested that seasonal influenza vaccination during pregnancy reduces the risk of lab-confirmed influenza infection in pregnant persons prior to delivery and up to 6 months post-partum (pooled VE=50%, 95% CI: 22 to 68%, I^2=49.22%). The results suggest that the benefit of seasonal influenza vaccination was similar from delivery to 6 months post-partum (pooled VE=57%, 95% CI: 14 to 78%, I^2=35.88%) compared to the period between enrollment and delivery (pooled VE=54%, 95% CI: -48 to 86%, I^2=72.28%). One (1) prospective cohort study conducted during the 2019-2020 influenza season in Greece also found a protective effect of seasonal IIV4 against LCI infection in pregnant persons (adjusted VE [aVE]=43.5%, 95% CI: 28.4 to 55.6%) [46].

Figure 1. Meta-analysis of RCTs reporting maternal lab-confirmed influenza from enrolment to 6 months post-partum comparing seasonal influenza vaccine to placebo or active comparator



A MA of 2 test-negative studies suggested that seasonal influenza vaccination during pregnancy reduces the risk of hospitalization due to lab-confirmed influenza in pregnant persons prior to delivery and up to 42 days post-partum (pooled aVE=42%, 95% CI: 19 to 58%, I^2=0%) [44, 47].

Figure 2. Meta-analysis of studies using test-negative study designs reporting maternal LCI hospitalization during pregnancy or 42 days post-partum among those vaccinated and unvaccinated against influenza during pregnancy



One (1) prospective cohort study reported VE of 38% (95% CI: 14 to 55%) against LCI hospitalization during pregnancy or up to 2 days after delivery [48].

Together, these studies suggest that seasonal influenza vaccination during pregnancy reduces the risk of LCI infection and hospitalization due to LCI during pregnancy and up to 6 months post-partum.

IV.2.2 Infant benefits: Vaccine efficacy/effectiveness outcomes

Summary of study characteristics

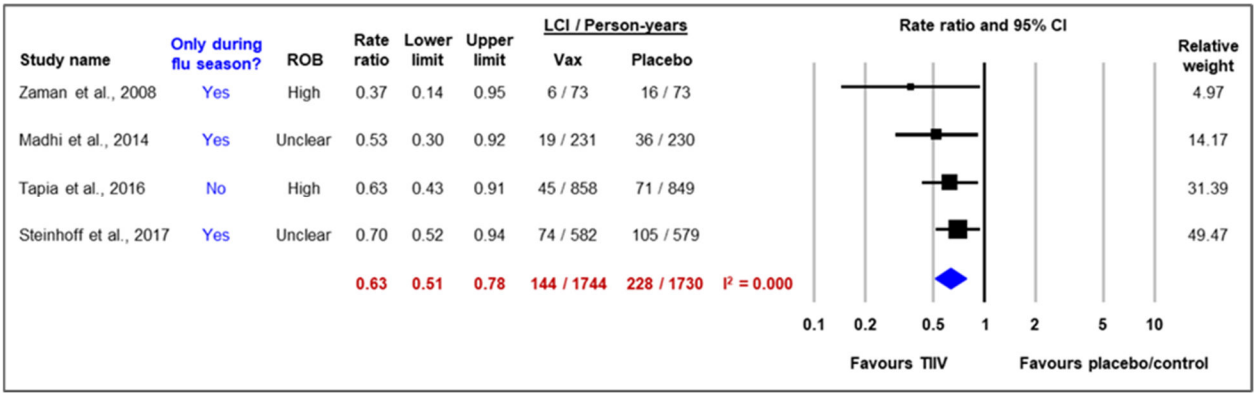
Overall, 7 studies reported data on LCI infection. Among those, 4 RCTs compared the efficacy of IIV to placebo (n=2) [40, 53] or active comparators (n=2; pneumococcal [43] or meningococcal vaccine [42]) during pregnancy against LCI infection in infants up to 6 months of age. 3 cohort studies identified from the updated literature search compared the effectiveness of seasonal influenza vaccination during pregnancy against LCI infection in infants up to 6 months of age [46, 49, 50].

A total of 5 studies (3 test-negative studies, including one identified from the DSEN SR [45, 47, 51], and 2 cohort studies [49, 50]) reported data on the effectiveness of influenza vaccination during pregnancy on hospitalization due to LCI infection in infants up to 6 months of age.

Summary of vaccine efficacy/effectiveness

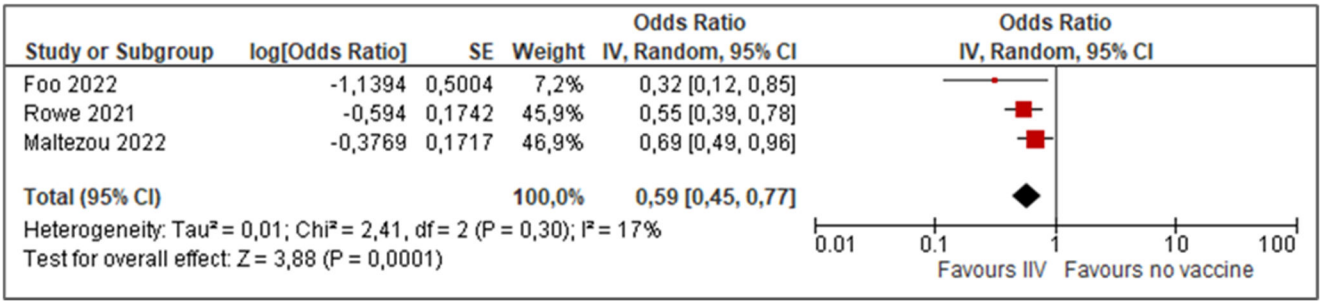
A MA of the 4 RCTs demonstrated a protective effect of seasonal influenza vaccination during pregnancy against LCI infection in infants up to 6 months of age (pooled VE=37%, 95% CI: 22 to 49%, I^2=0.00%) . Results from the RCTs suggest that the greatest effect of seasonal influenza vaccination during pregnancy against LCI infection in infants was found from birth up to 2 months of age (pooled $VE_{0 \text{ to } \leq 2 \text{ months}}$=61%, 95% CI: 17 to 81%, I^2=39.57%), following which the protective effect of vaccination during pregnancy waned as infant age increased (pooled $VE_{2 \text{ to } \leq 4 \text{ months}}$=42%, 95% CI: -13 to 70%, I^2=59.67% and pooled $VE_{4 \text{ to } \leq 6 \text{ months}}$=24%, 95% CI: -3 to 44%, I^2=0.00), a biologically plausible finding due to the waning of the effects of passive transfer of antibodies in neonates.

Figure 3. Meta-analysis of RCTs reporting infant LCI among infants born to pregnant persons vaccinated against influenza or receiving a placebo or active control during pregnancy



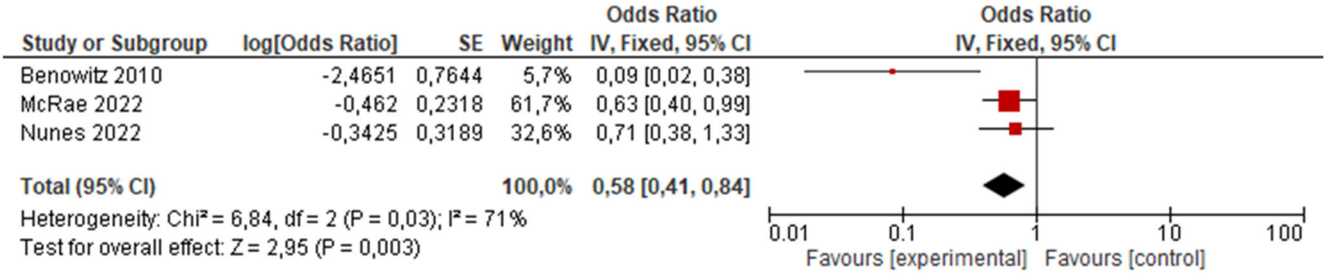
A MA of the 3 cohort studies demonstrated a protective effect of seasonal influenza vaccination during pregnancy against LCI infection in infants up to 6 months of age (pooled aVE=41%, 95% CI: 23 to 55%, I^2=17%) [46, 49, 50].

Figure 4. Meta-analysis of cohort studies reporting infant LCI among infants born to pregnant persons vaccinated and unvaccinated against influenza during pregnancy



A MA of the 3 test-negative studies demonstrated a protective effect of seasonal influenza vaccination during pregnancy against hospitalization due to LCI infection in infants up to 6 months of age (pooled aVE=42%, 95% CI: 16 to 59%, I^2=71%) [45, 47, 51]. Two (2) cohort studies reported data on hospitalization due to LCI infection in infants up to 6 months of age, but only one demonstrated a significant protective effect of influenza vaccination during pregnancy (aVE, 95% CI: 62%, 9 to 84% [49], and 21%, 95% CI: -18 to 47% [50]).

Figure 5. Meta-analysis of studies using test-negative study designs reporting laboratory-confirmed influenza hospitalization in infants up to 6 months of age born to pregnant persons vaccinated or unvaccinated against influenza during pregnancy



Together, these studies suggest that seasonal influenza vaccination during pregnancy reduces the risk of LCI infection and hospitalizations due to LCI infection in infants up to 6 months of age.

IV.3 Vaccine safety

Summary of study characteristics

The DSEN SR on the safety of influenza vaccination during pregnancy evaluated non-obstetric serious adverse events (SAE) in pregnant persons related to the administration of seasonal influenza vaccination during pregnancy using findings from 3 RCTs and 3 cohort studies. Additionally, the SR included 4 RCTs and 24 observational studies, including 20 cohort and 4 case-control studies, addressing other safety and/or pregnancy/birth related outcomes (i.e., infant death, spontaneous abortion, stillbirth, preterm birth, SGA, low birth weight and congenital anomalies). Outcomes of seasonal influenza vaccination were compared with those for other vaccines (e.g., meningococcal, or pneumococcal vaccines), placebo or no vaccination.

Eleven (11) additional observational studies were identified from the updated literature search evaluating non-obstetric SAEs/AEs and other safety and/or pregnancy/birth outcomes (i.e., spontaneous abortion, stillbirth, preterm birth, SGA, low birth weight and congenital anomalies) related to the administration of influenza vaccine during pregnancy. Of those, 3 were single-arm cohort studies and one was a case series derived from registries of AEs of interest. These study designs were not included in the DSEN SR, but were included in the updated literature search to capture studies reporting data on the safety of administration during pregnancy of more recently licensed influenza vaccines that are based upon new different technologies, including quadrivalent mammalian cell culture-based vaccines (e.g., IIV4c; Flucelvax® Quad) and RIV (e.g., quadrivalent recombinant influenza vaccines [RIV4]; Supemtek™), given the limited published peer-reviewed evidence on these vaccines.

Summary of vaccine safety

IV.3.1 Harms to the pregnant person: Non-obstetric serious adverse events in pregnant people

Serious systemic reactions within 7 days of vaccination

Two (2) RCTs evaluated the risk of severe systemic reactions within 7 days of seasonal influenza vaccination in pregnant people. One (1) RCT conducted in South Africa by Madhi et al. (2014) found 27 of 181 people who received trivalent IIV (IIV3) (14.9%) and 19 of 172 who received a saline placebo (11.0%) experienced at least one severe systemic reaction, which included severe weakness/tiredness, headache, fever, joint pain, and muscle pain, within 7 days of vaccine administration [41]. A larger RCT conducted in Mali by Tapia et al. (2016) found that 2 of 2,105 women who received IIV3 (0.1%) and none of the 2,082 people who received meningococcal vaccine (0.0%) experienced a severe systemic adverse reaction within 7 days of vaccine administration [42]; the 2 severe reactions included febrile sensation and headache, and it was unclear whether those 2 events occurred in the same participant. No significant difference in the frequency of severe systemic reactions within 7 days of seasonal influenza vaccination was observed within each individual study (RR=1.35, 95% CI: 0.78 to 2.34 [41], and RR= 4.95, 95% CI: 0.24 to 102.95 [42]); pooled estimates were not calculated given the substantial differences in the risks of SAEs in the intervention groups of the 2 studies and the control groups. There were likely unknown differences in outcomes definitions or other sources of heterogeneity.

Other serious non-obstetric adverse events

Two (2) RCTs, 6 cohort studies and 1 case-series reported data on other non-obstetric SAEs. One (1) RCT conducted by Madhi et al. (2014) found no difference in the occurrence of non-obstetric SAEs that were possibly or probably related to influenza vaccination within 30 days of vaccination administration (1 in 1,062 IIV3 and 0 in 1,054 saline placebo recipients; RR=2.98, 95% CI: 0.12 to 73.01) [41]. Another RCT conducted by Zaman et al. (2008) reported data on peripartum hospitalizations due to non-obstetric causes, with no apparent difference between IIV3 and pneumococcal vaccine recipients (1 event in 159 IIV3 and 2 events in 157 pneumococcal vaccine recipients; RR=0.49, 95% CI: 0.05 to 5.39) [43].

Five (5) cohort studies reported non-obstetric SAEs either within 42 days of vaccination or within an unknown time period. In an American study, Munoz et al. (2005) found 2 hospitalization events unrelated to pregnancy in 225 vaccinated pregnant persons and 3 in 826 unvaccinated pregnant persons within 42 days of intervention, with none related to vaccination (RR=2.45, 95% CI: 0.41 to 14.56) [54]. The cause of hospitalization included influenza illness with emesis and migraine headache in the vaccinated group, and influenza with emesis, appendicitis, and calculus ureter-stent replacement in the unvaccinated group. Finally, 4 cohort studies did not report any SAEs after the administration of IIV4 (Fluzone® Quadrivalent) [55], IIV4-cc (Flucelvax® Quad) [56] and IIV3 during pregnancy [57, 58].

Guillain-Barré syndrome

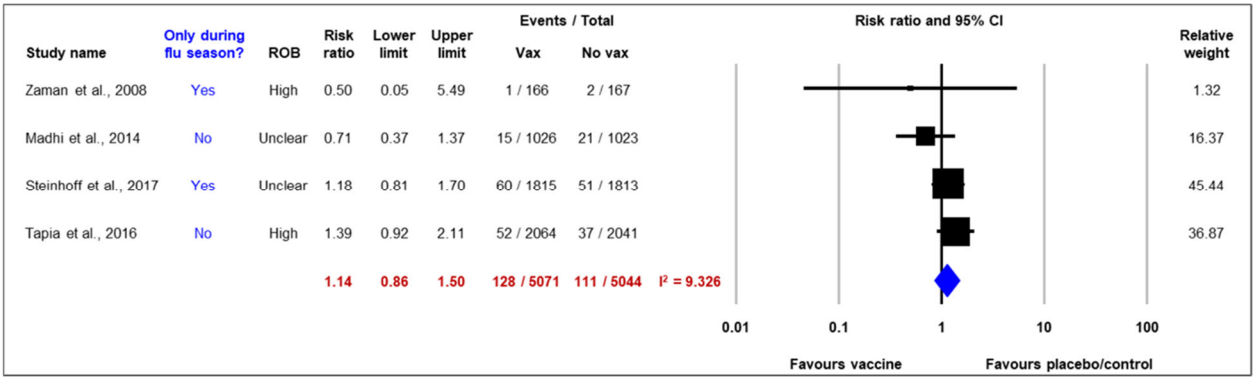
One (1) cohort study and 1 case-series reported data on Guillain-Barré syndrome following seasonal influenza vaccination during pregnancy. Within 42 days of intervention, Nordin et al. (2013) identified no inpatient cases of Guillain-Barré syndrome in 75,906 vaccinated pregnant persons and 1 case in 147,992 unvaccinated pregnant persons in the USA (RR=0.65, 95% CI: 0.03 to 15.95) [59]. One (1) case series identified from the updated literature search reported 1 case (n=239) of Guillain-Barré syndrome that occurred 5 days after IIV4 administration during the third trimester of pregnancy in a 29-year-old woman. The woman gave birth to a healthy baby while recovering and has fully recovered [60].

These studies suggest that pregnant persons vaccinated with seasonal influenza vaccines during pregnancy appear to experience the same rates of non-obstetric serious AEs as non-pregnant persons vaccinated with seasonal influenza vaccines, pregnant persons vaccinated with pneumococcal or meningococcal vaccines, as well as unvaccinated pregnant persons.

IV.3.2 Infant harms: Infant death from 0 to 6 months of age

Four (4) RCTs compared the effect of seasonal influenza vaccination to placebo (n=2) [40, 41] or active comparators (n=2; meningococcal quadrivalent vaccine [42] or 23-valent pneumococcal vaccine [43]) during pregnancy on infant death up to 6 months of age. All RCTs were conducted in low-to-middle-income countries, and the control group infant death risk ranged from 1.1% and 2.8%. A MA of these RCTs did not demonstrate an association between seasonal influenza vaccination during pregnancy and infant death (pooled RR=1.14, 95% CI: 0.86 to 1.50, I^2 = 9.33).

Figure 6. Meta-analysis of RCTs reporting infant death up to 6 months of age among infants born the pregnant persons vaccinated or unvaccinated against influenza during pregnancy



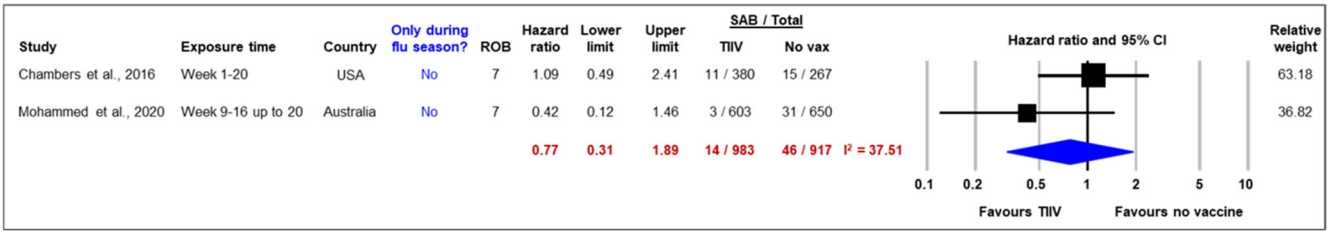
No infant death was reported from a prospective cohort study conducted in Japan among infants diagnosed with fever from 0 to 6 months of age born from vaccinated and unvaccinated pregnant people (0/36 IIV3 and 0/47 unvaccinated) [61].

These studies suggest that seasonal influenza vaccination during pregnancy is not associated with infant death up to 6 months of age.

IV.3.3 Infant harms: Spontaneous abortion

Three (3) cohort studies and 3 observational studies evaluated the effect of IIV during pregnancy on spontaneous abortion (SAB) under 20 and 22 weeks gestational age. Two (2) prospective cohort studies were included in a MA and no association between IIV and SAB was demonstrated (pooled adjusted hazard ratio [aHR]=0.77, 95% CI: 0.31 to 1.89, I^2=37.51%) [62, 63]. A third prospective cohort study conducted in Japan found the same risk of SAB under 22 gestational weeks (0.4%) among unvaccinated and vaccinated pregnant people (first-trimester vaccination) [64].

Figure 7. Meta-analysis of cohort studies reporting spontaneous abortion among pregnant persons vaccinated and unvaccinated against seasonal influenza during pregnancy



Two (2) retrospective case-control studies conducted by the same set of investigators in the US assessed the association between SAB and vaccination within 28 days prior to SAB. The first study was conducted over 2 consecutive influenza seasons following the 2009 H1N1 pandemic [12]. The authors observed an increased risk of SAB following IIV only in the first post-pandemic season (2010-2011 adjusted odds ratio [aOR] = 3.70, 95% CI: 1.40 to 9.40) but not the second (2011-2012 aOR=1.40, 95% CI: 0.60 to 3.30). Post-hoc analyses of 2010-2011 data found that people who had been previously vaccinated in the 2009-2010 season with the H1N1 pandemic vaccine were at increased risk of SAB following IIV in the 2010-2011 season, which was not observed in those not vaccinated with the H1N1 pandemic vaccine in 2009-2010 but vaccinated with IIV in 2010-2011.

The second study conducted over 3 consecutive influenza seasons (i.e., 2012-2013, 2013-2014 and 2014-2015) by Donahue, et al. (2019) sought to confirm the association observed between SAB and history of influenza vaccination [65]. No association was found between seasonal influenza vaccination during pregnancy and SAB within 28 days of vaccination (aOR = 0.80, 95% CI: 0.60 to 1.10), including among people vaccinated in the previous season. The authors state that the association of prior season vaccination found in the initial study may have been a spurious result due to residual confounding or random error, or it may have been due to differences in the time periods of the 2 studies. One (1) cohort study identified from the updated literature search conducted in the US over the 2008-2009 to 2013-2014 influenza seasons did not find an association between the history of pandemic H1N1 containing influenza vaccination and spontaneous abortion within 28 days of vaccination (aHR=1.19, 95% CI: 0.97 to 1.46) [66].

Three (3) additional single-arm cohort studies and 1 case series identified from the updated literature search reported data on SAB in persons vaccinated with IIV during pregnancy. The 1 case-series study described SABs after vaccine exposure that were reported from several countries to the Fluzone® Quadrivalent (IIV4, Sanofi) Pregnancy Registry from 2013 to 2019. Four (4) SABs were captured by the pregnancy registry; however, the frequency of neonatal adverse outcomes presented in the study are consistent across the literature and do not exceed the expected rates in the general population. One (1) cohort study described SABs identified among IIV-exposed pregnancies that were reported to the US registry or through GSK worldwide safety database. From the US registries, 3 spontaneous abortions were reported from 115 pregnancies. From the 3 SABs reported, there were 2 SABs in which exposure occurred during the first trimester, and 1 for which the date of exposure was unknown. From the worldwide database, 26 out of 676 reports of influenza vaccine exposure during pregnancy resulted in SABs; however, there was no information on exposure timing. SABs originate during the first and second trimesters of pregnancy (i.e., at risk periods), therefore, exposures occurring in the third trimester are not likely to be causally associated. Two (2) prospective cohort studies that were conducted to fulfill a post-marketing commitment to the US Food and Drug Administration (FDA) evaluated the safety of IIV4 (Afluria® Quadrivalent) and IIV4-cc (Flucelvax® Quadrivalent) administrated during pregnancy. The studies reported 2.5% and 1.9% SABs after administration of IIV4 and IIV4-cc during the first trimester of pregnancy, respectively, which was not increased when compared to the rate in the general US population. Overall, from the 3 single-arm cohort studies and the case series study, no safety signals were identified among pregnant persons exposed to IIV.

One (1) cohort study did not observe a significant association between immunization with a pandemic H1N1-containing influenza vaccine prior to 21 6/7 weeks' gestation and spontaneous abortion, regardless of the vaccine received in the prior influenza season (i.e., pandemic H1N1-containing influenza vaccine or non-pandemic-H1N1-containing influenza vaccine) [66].

Together, these studies suggest that seasonal influenza vaccination during pregnancy does not appear to be associated with an increased risk of spontaneous abortion.

IV.3.4 Infant harms: Other birth outcomes

No safety issues were identified regarding the administration of seasonal influenza vaccines during pregnancy, with respect to other adverse birth outcomes including stillbirth (≥18-22 gestational weeks or ≥500g); preterm birth; SGA; low birth weight; and congenital anomalies identified at birth or up to 6 months of age. Evidence was derived from both RCTs and observational studies, including case-control studies and cohort studies. Limited published peer-reviewed evidence regarding the safety of administration during pregnancy of more recently licensed influenza vaccines that are based upon new different technologies, including mammalian IIV-cc (e.g., IIV4-cc; Flucelvax® Quad) and RIV (e.g., RIV4; Supemtek™) was identified. Details on other adverse birth outcomes are available in Table 1 (Summary of Evidence).

V. ETHICS, EQUITY, FEASIBILITY AND ACCEPTABILITY CONSIDERATIONS

V.1 Ethics considerations

NACI evaluated the following ethical considerations when making its recommendations: promoting well-being and minimizing risk of harm; maintaining trust; respect for persons and fostering autonomy; and promoting justice and equity. NACI also identified the ethical imperative to protect the public's health and the health of the most vulnerable. NACI addressed the identified ethical considerations throughout the vaccine guidance development process and these considerations have been incorporated into the recommendations.

V.2 Equity considerations

No distinct inequities that may arise because of the recommendations were identified. However, the following intersectional factors described in NACI's EEFA framework were considered: pre-existing conditions; social factors; place of residence; and access to healthcare.

Pregnant individuals and individuals with chronic health conditions are identified among the groups at greater risk of influenza-related complications or hospitalization [(1)]. Racialized people and Indigenous people may also be at increased risk for severe influenza disease due to a variety of intersecting factors, including underlying medical conditions and potentially decreased access to healthcare resources. Canadians with low household incomes, unstable or crowded housing, and individuals living in remote or rural areas may face increased exposure to influenza and challenges accessing healthcare [(36)]. Gender-diverse pregnant people are more likely to face discrimination or poor treatment in medical settings and may be more reluctant to seek healthcare. Individuals such as international students and newcomers to Canada may face language barriers in accessing healthcare.

V.3 Feasibility considerations

Based on the feasibility matrix NACI completed as part of its EEFA analysis, there were no distinct, significant issues identified for feasibility with respect to resource and integration implications that could impact decision making for this recommendation since this is an existing immunization program. Recommendations that allow vaccination at all gestational stages of pregnancy would reduce feasibility barriers in vaccination programs.

V.4 Acceptability considerations

NACI evaluated the following acceptability considerations when making its recommendations: individual beliefs; values and knowledge; socio-demographic factors; and systemic factors. Refusing vaccination during pregnancy is common globally, resulting in a low vaccine coverage

rate [70]. Low vaccine uptake in pregnant individuals has been partly attributed to vaccine hesitancy, which is complex and multidimensional and can be influenced by individual, logistical, cultural, and sociologic factors.

A pregnant individual's beliefs, values, and knowledge about seasonal influenza and vaccination affect the acceptance of vaccination during pregnancy [70, 71]. Individuals who believe the vaccines to be safe and effective and individuals who perceive themselves to be at risk of seasonal influenza and have the desire to protect others against the virus are more likely to pursue vaccination [70-73]. Conversely, pregnant individuals are less likely to pursue vaccination if they have anti-vaccination beliefs and concerns regarding the effects of vaccination on the health of the individual and fetus, and limited knowledge regarding the risks of influenza and the benefits of vaccination during pregnancy [70, 71, 73]. In the 2021 Canadian Survey on Vaccination During Pregnancy Study (SVP), 51% of participants responded that their reason for not getting the influenza vaccine during pregnancy was "not wanting to be vaccinated during pregnancy" [36]. Furthermore, evidence from Okoli et al. (2021) suggests a potential vulnerability of multiparous women with respect to the uptake of preventive care [74], as they may assume that their current pregnancy will be uneventful because previous pregnancies were uneventful and may become complacent about vaccination. These data suggest that programs designed to enhance pregnant individuals' information and vaccine literacy may promote greater seasonal influenza vaccine acceptance during pregnancy [74]. Additionally, it is important to note that in 2021, the SVP reported a significant increase (53%) in influenza vaccination among pregnant individuals since the 2019 survey (45%) [36].

Systemic factors contribute to the acceptability of seasonal influenza vaccination among pregnant individuals. Systems and policies or delivery models that promote universal access to vaccines are most effective at improving uptake and coverage in the Canadian context [72]. Healthcare providers also play an important role in offering the influenza vaccine and positively influencing pregnant individuals' perceptions of seasonal influenza vaccination [70, 71, 73, 75, 76]. Increased access to trusted healthcare providers who inform pregnant individuals of the benefits and recommendations of seasonal influenza vaccination during pregnancy is associated with increased acceptability [77]. Qiu et al. (2021)'s internationally sourced SR findings suggest that a healthcare provider's recommendation was a main facilitator of vaccine acceptability among pregnant individuals, and its absence was the main barrier reported among unvaccinated women [78]. Blanchard-Rohner et al. (2012) found in their Switzerland based study that most past-partum people neither recalled being recommended vaccination nor informed about the risks of influenza during pregnancy [79]. Evidence from the SVP study (2021) supports these conclusions in the Canadian context with the proportion of women vaccinated against influenza during pregnancy being substantially higher among women who received a recommendation to be vaccinated (70%), compared to those who did not receive a recommendation to be vaccinated (14%) [36]. Providers' knowledge and beliefs about the influenza vaccine, their experiences supporting pregnant individuals, as well as their workload and time constraints, affect their practices in advocating for the influenza vaccine during pregnancy [80]. These findings suggest that improved access to healthcare providers who are well informed and can communicate the importance of seasonal influenza during pregnancy is the most likely way to increase vaccine acceptability.

Impact of COVID-19 pandemic on vaccination during pregnancy

The COVID-19 pandemic has affected the acceptability of vaccination and seasonal influenza vaccination. The Childhood National Immunization Coverage Survey (CNICS) collects information on national immunization coverage for vaccines administered to children and pregnant individuals. Data from the CNICS released in December 2022 showed the proportion of pregnant people who were more inclined to get vaccinated as a result of the pandemic varied across provinces and territories, from a low of 9% (Quebec) to a high of 32% (Yukon). Survey results also showed that the pandemic increased intent to receive vaccination among racialized groups; for example, a significantly higher proportion of Filipino Canadians (39%) and South Asian Canadians (26%) were more inclined to get vaccinated as a result of the pandemic relative to non-Indigenous and non-racialized people (14%) [81]. Furthermore, the SVP study (2021) identified systematic barriers to receiving vaccinations in Canada in the context of the COVID-19 pandemic. This survey (2021) found that 11% of the pregnant individuals surveyed reported that they encountered an obstacle or delayed vaccination during the COVID-19 pandemic. Of those, 73% reported limited appointment availability, 40% were concerned about being exposed to COVID-19, 25% reported a lack of walk-in options, and 12% received recommendations from a doctor or local public health authority to delay vaccination [36].

VI. DISCUSSION

The present SR and MA examined current literature on the use of influenza vaccines during pregnancy. Findings from this review suggest that influenza vaccination during pregnancy is effective in reducing the risk of LCI infection and hospitalization in both pregnant individuals and their infants up to 6 months post-partum. Overall, the evidence from this review indicates that seasonal influenza vaccine efficacy and effectiveness in pregnant individuals appear to be comparable to the general population of healthy adults and consistent with VE point estimates reported in a previous MA by Osterholm, et al. (2012) [82].

The evidence also suggests that influenza vaccination during pregnancy does not increase the risk of non-obstetric SAEs in pregnant persons; infant death; spontaneous abortion; stillbirth; pre-term birth; small for gestational age; low birth weight; and congenital anomalies. In fact, some studies suggested a protective effect of influenza vaccination for stillbirth [83-85] and low birth weight [63, 86-89].

The SR and MA findings are in accordance with other reviews that have been undertaken to evaluate the efficacy/effectiveness of influenza vaccination during pregnancy [15, 16, 90]. By comparison, the SR, and MA by Quach et al. (2020) reported similar protective effects of seasonal influenza vaccine against LCI in pregnant persons (RR=0.15, 95% CI: 0.06 to 0.36 and OR=0.37, 95% CI: 0.23 to 0.61) [16]. Moreover, Nunes et al. (2017) and Jarvis et al. (2020) consistently reported similar protective effects, with meta-analyses demonstrating a reduction in the risk of LCI in infants born to the vaccinated parent (RR=0.52, 95% CI: 0.41 to 0.67 [90] and RR=0.66, 95% CI: 0.50 to 0.85 [15]). Minor differences in the pooled results from the findings of the present review may be attributed to variations in the study inclusion criteria, MA methods and other factors.

The findings of this SR are also consistent with previous reviews that investigated the safety of influenza vaccines administered during pregnancy and found no significant association with increased safety risk [13-16, 90, 91]. Particularly, Minozzi et al. (2022) and Hansen et al. (2021) reported pooled estimates that support the present review's findings, demonstrating a lack of association between the influenza vaccine and infant death (RR=1.24, 95% CI: 0.96 to 1.60 [13] and RR=1.11, 95% CI: 0.87 to 1.41) [14]. Furthermore, current evidence suggests that there are no adverse early childhood health outcomes associated with influenza immunization during pregnancy [92-94].

Despite similarities in the estimates of efficacy and effectiveness of influenza vaccines during pregnancy, limitations in the included studies in this review should be noted. Firstly, adjustment for confounding was not consistently conducted in the observational studies, nor was accounting for immortal time bias for time-dependent outcomes. With respect to study design, there was high variability in the outcome definitions and the time points for some outcomes. Furthermore, it was unclear if some RCT outcomes could be generalized to the Canadian context. Finally, assumptions were made regarding equivalence of effect estimates and for VE estimates, as the concordance of influenza vaccine strains with circulating strains was not considered.

Beyond the scope of this review, a wide range of additional influenza vaccine efficacy/effectiveness and safety outcomes regarding influenza vaccination during pregnancy

have been systematically explored in the literature. For example, Jarvis et al. (2020) and Quach et al. (2020) assessed influenza vaccine efficacy/effectiveness during pregnancy by investigating the incidence of influenza-like illness (ILI) and other respiratory illnesses [15, 16]. Conversely, Hansen et al. (2021) assessed seasonal influenza vaccine safety by reporting on non-influenza infectious AEs, all-cause mortality, and mortality from presumed infectious causes [14], whereas Jarvis et al. (2020) reported long-term respiratory conditions (asthma) [15].

Studies considering the impact of timing of influenza vaccination on protection of the pregnant individual and fetus/newborn are limited. A 2019 SR and MA on optimal timing on influenza vaccination during pregnancy found that individuals vaccinated later during pregnancy had a greater immune response to vaccination and increased antibody transfer to the fetus [95]. However, prioritizing vaccination during a later gestational age could leave the pregnant person vulnerable to influenza infection for a significant proportion of the pregnancy and may be challenging to implement programmatically.

NACI will continue to monitor the evidence base and will update its guidance as needed.

VII. RECOMMENDATIONS

Following the review of available evidence summarized above, as well as the assessment of EFFA considerations with the EEFA Framework, the following section outlines the evidence-informed recommendations made by NACI regarding influenza vaccination in pregnancy. NACI will continue to carefully monitor the scientific developments related to influenza vaccines, as well as ongoing vaccine pharmacovigilance, and will update its recommendations as required. Additional information on the strength of NACI recommendations is available in Table 4.

The following recommendation for influenza vaccination in pregnancy supplements NACI's overarching recommendations for influenza vaccination, which are 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 6 months of age and older ***(Strong NACI Recommendation)***, noting product-specific contraindications.

1. **NACI recommends that influenza vaccine should be offered to pregnant individuals. Recommended products include: IIV-SD, IIV-cc, and RIV. *(Strong NACI Recommendation)***

    - There has been no identified safety signal regarding the use of RIV during pregnancy although published clinical data are limited.
    - There has been no identified safety signal regarding the use of LAIV in pregnancy, although there are more data on the safety of other influenza vaccine products in pregnancy. There is also evidence that IIV has higher efficacy than LAIV in healthy adults. Note that vaccination with LAIV during pregnancy should not be considered a reason to terminate pregnancy.
    - The only adjuvanted vaccine in Canada for the 2023/2024 influenza season is the adjuvanted inactivated trivalent influenza vaccine (IIV3-Adj), which is authorized for infants 6 to 23 months (Fluad Pediatric®) and adults 65 years and older (Fluad®). There has been no identified safety signal regarding adjuvanted influenza vaccines in pregnancy; however, IIV3-Adj is not authorized for people of reproductive age.
    - The only high-dose vaccine in Canada for the 2023/2024 influenza season is the high-dose inactivated quadrivalent influenza vaccine IIV4-HD (Fluzone® High-Dose Quadrivalent) which is authorized for adults 65 years and older. There has been no identified safety signal regarding high-dose influenza vaccines in pregnancy, however, IIV4-HD is not authorized for people of reproductive age.

Summary of evidence and rationale:

- The safety of influenza vaccination during pregnancy is consistently supported by numerous studies, including clinical trials and observational studies, and routine pharmacovigilance data from safety reporting systems.
- Published data, including currently available studies of fetal death, spontaneous abortion, and congenital malformations, do not report unexpected or concerning patterns. The evidence reaffirms that seasonal influenza vaccination during pregnancy does not appear

to be associated with significant safety issues with respect to adverse birth outcomes or maternal non-obstetric SAEs.
- Published data continue to demonstrate the efficacy/effectiveness of influenza vaccination during pregnancy for protection against LCI infection and to help mitigate the severity of influenza infection.
- The efficacy/effectiveness of seasonal influenza vaccination in pregnant individuals is comparable to the general adult population.
- Studies have demonstrated that infants receive protection from maternal antibodies as a result of influenza vaccination during pregnancy, and their results suggest that seasonal vaccination during pregnancy reduces the risk of LCI infections and LCI hospitalizations in infants up to 6 months of age.

2. NACI recommends that influenza vaccination should be offered at any stage of pregnancy (i.e., in any trimester). *(Strong NACI recommendation)*

- If an individual's pregnancy extends over 2 influenza seasons, that person may receive 2 doses of influenza vaccine (i.e., one dose in each season, during the course of the pregnancy).

Summary of evidence and rationale:

- There is insufficient evidence to establish the optimal timing of influenza vaccination for maternal or fetal/newborn outcomes.
- Prioritizing vaccination during a specific gestational stage may lead to programmatic challenges and missed vaccination opportunities.

3. NACI recommends the inclusion of all pregnant individuals, at any stage of pregnancy, among those who are particularly recommended to receive influenza vaccination. *(Strong NACI recommendation)*

Summary of evidence and rationale:

- The evidence consistently shows an association between pregnancy and increased disease severity with influenza infection. This includes hospitalization, admission to the ICU, invasive mechanical ventilation, and maternal mortality.
- There is also a higher risk of adverse neonatal outcomes (e.g., premature delivery, low birth weight, NICU admission) with influenza infection during pregnancy.
    - The risks for preterm delivery, low birth weight and admission to the NICU increase with disease severity in the pregnant person.
- Infants under 6 months are at increased risk of hospitalization due to influenza infection compared to children from other ages. However, influenza vaccine is not effective in infants under 6 months; therefore, passive immunization of fetuses through transplacentally transmitted anti-influenza antibodies is currently the best available prevention strategy.
- Despite the increased risks of severe disease there is a suboptimal uptake of influenza vaccination during pregnancy in Canada, with only approximately 53% of pregnant individuals receiving the vaccine in 2021.

- Among pregnant people, there is a disproportionate burden of disease and low vaccine uptake among those who are racialized, Indigenous, younger, low-income, and/or living in rural settings.

4. **NACI reiterates its recommendation that influenza vaccination may be given at the same time as, or at any time before or after administration of another vaccine, including COVID-19 or pertussis vaccine.** ***(Strong NACI recommendation)***

- Every appropriate opportunity to immunize during pregnancy, with any immunization for which the pregnant person is eligible, should be taken.

Summary of evidence and rationale:

- No known safety signal for concurrent administration of influenza with another vaccine during pregnancy has been identified.
- Administration of multiple vaccines at the same visit is a strategy for increasing immunization uptake.

VIII. RESEARCH PRIORITIES

- Study the longer-term outcomes of infants and children exposed to influenza infection in-utero.
- Research on seasonal influenza illness and vaccination rates among pregnant individuals and infants outside of a 2009 H1N1 pandemic context, particularly during/following the COVID-19-pandemic.
- Collect national-level influenza surveillance data for pregnant individuals and infants under 6 months of age in Canada will help to better define the burden of disease for pregnant people and infants.
- Study the longer-term outcomes for children born to individuals vaccinated during pregnancy.
- Collect additional safety data for newer vaccine technologies, including cell culture and RIV.
- Study the timing of influenza immunization in pregnant individuals with respect to duration or waning of protection against infection and severe disease.
- Examine vaccine confidence and acceptability among pregnant individuals in Canada, especially among racialized groups.
- Investigate range and complex interplay of factors that influence acceptability of influenza immunization in general and for high-risk groups (including pregnant individuals).
- Study the COVID-19 pandemic's potential ongoing impact on vaccine hesitancy and maternal vaccine uptake.
- Learn more about patient, provider, and system-level barriers to vaccination in pregnancy in Canada, including:
    - Policy and structural factors;
    - Patients' knowledge, understanding and beliefs about influenza vaccination during pregnancy, especially given the heterogeneity of Canada's population (i.e., differences in socioeconomic and cultural backgrounds and differences in trust in the medical system).

IX. SURVEILLANCE PRIORITIES

Ongoing and systematic data collection, analysis, interpretation, and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-based decision-making. To support such efforts, NACI encourages ongoing surveillance and continued expansion of surveillance details in the epidemiology of influenza in Canada.

Overall, there is a gap in knowledge on the impact of seasonal influenza among pregnant persons and perinatal/postnatal outcomes in Canada and worldwide. To date, most epidemiological studies have focused on the 2009 H1N1 pandemic in certain high-income countries (e.g., US) and report inconsistent findings on the association between influenza illness and adverse perinatal outcomes. There is also a shortage of studies conducted after the COVID-19 pandemic, beginning in late 2019/early 2020. Therefore, more updated surveillance on seasonal influenza among pregnant persons and young infants in low, medium, and high-income countries, including Canada, is needed to better understand the burden of disease and develop targeted vaccine campaigns for these high-risk groups.

In Canada, FluWatch, the national surveillance system, monitors the spread of influenza and ILI by province/territory and age group, but does not specify pregnancy status. Therefore, initiatives are needed to collect influenza information (e.g., ILI incidence, viral strain, hospitalization) from pregnant persons to inform appropriate public health efforts such as targeted vaccination campaigns and education.

X. TABLES

Table 1. Summary of Evidence

						Summary	
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**	**Level of evidence**	**Quality**
Vaccine efficacy							
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022 [18] Funded by the Canadian Institutes of Health Research (CIHR) and the Drug Safety and Effectiveness Network (DSEN)	Lab-confirmed influenza (LCI) assessed by RT-PCR during pregnancy and up to 6 months post-partum.	IIV3 (Vaxigrip®, Sanofi) Placebo Active control: Meningococcal quadrivalent vaccine (Menactra®, Sanofi Pasteur)	RCTs [40-42] Countries: Nepal (n=1) Mali (n=1) South Africa (n=1) Follow-up: Not restricted to influenza season between 2011 and 2014 (n=2) One RCT was restricted to the 2011-2012 and 2012-2013 influenza seasons [40] Funding: Non-industry (n=3)	Pregnant persons (n=10,074) IIV3: n=5,089 (50.5%) Placebo or active control: n=4,985 (49.5%)	The MA included 3 RCTs. The pooled vaccine efficacy was 50% (95% CI: 22 to 68%), I^2=49.22%.	Level I	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022 [18].	Laboratory-confirmed influenza (LCI) assessed by RT-PCR in infant up to 6 months of age.	IIV3 (Vaxigrip®, Sanofi and Fluarix, GSK) Placebo	RCTs [40-43] Countries: Bangladesh (n=1) South Africa (n=1) Mali (n=1) Nepal (n=1)	Infants up to 6 months of age (n=3,474) IIV3: n=1,744 (50.2%)	The MA included 4 RCTS. The pooled vaccine efficacy was 37% (95%	Level I	Fair

Funded by the CIHR and the DSEN		Active control: Meningococcal quadrivalent vaccine (Menactra®, Sanofi Pasteur) and Pneumococcal vaccine, 23-valent (Pneumovax® 23, Merck)	Follow up: Not restricted to influenza season between 2004 and 2014 (n=3). One RCT was restricted to the 2011-2012 and 2012-2013 influenza seasons [40] Funding: Non-industry (n=3) and mixed funding (n=1).	Placebo or active control: n=1,730 (49.8%)	CI: 22 to 49%), I^2= 0.00%.		
Vaccine effectiveness							
Maltezou HC, Stavros S, Asimakopoulos G et al. Effectiveness of maternal vaccination with quadrivalent inactivated influenza vaccine in pregnant women and their infants in 2019-2020. 2022 [46] Funded by Sanofi	Lab-confirmed influenza assessed by RT-PCR during pregnancy.	IIV4 (VaxigripTetra®, Sanofi)	Prospective cohort study Country: Greece Follow up: 2019-2020 influenza season Funding: Industry	Pregnant persons 18 to 45 years of age (n=636): IIV4: n=406 (63.8%) Unvaccinated: n=230 (36.2%)	The aVE was 43.5% (95% CI: 28.4 to 55.6%).	Level II-2	Good
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN **And study identified from the update literature search:** **Nunes MC, Walaza S, Meiring S, et al.** Effectiveness of	Hospitalization due to LCI assessed by RT-PCR during pregnancy or up to 42 days post-partum.	IIV (Seasonal influenza vaccine)	TND studies (Thompson 2019 and Nunes 2022) [44, 47] Countries: Australia (n=1) Canada (n=1) United States (n=1) Israel (n=1) South Africa (n=1)	Pregnant persons (n=1,391). IIV: n=317 (22.8%) Unvaccinated: n=1,074 (77.2%)	The MA included 2 TND studies. The pooled aVE was 42% (95% CI: 19 to 59%), I^2=0.00%.	Level II-2	Good

influenza vaccination of pregnant women for prevention of maternal and early infant influenza-associated hospitalizations in South Africa: A prospective test-negative study. 2022 [47] Funded by the National Institute for Communicable Diseases of the National Health Laboratory Service; the US Centers for Disease Control and Prevention; and the Bill and Melinda Gates Foundation.			Follow up: 7 influenza seasons between 2010 and 2018 Funding: Non-industry (n=2)				
Vousden N, Bunch K, Knight M et al. Incidence, risk factors and impact of seasonal influenza in pregnancy: A national cohort study. 2021 [48] Funded by the National Institute for Health Research (NIHR)	Hospitalization due to LCI assessed by virological testing at any stage of pregnancy or up to 2 days after delivery.	IIV (Seasonal influenza vaccine)	Prospective cohort study Country: United Kingdom Follow up: Not restricted to the influenza season between 2016/11/01 to 2018/10/30 Funding: Non-industry	Individuals hospitalized at any stage of pregnancy or up to 2 days after delivery (n=1,099). IIV: n=320 (29.1%) Unvaccinated: n=466 (42.4%) Unknown/missing: n=313 (28.5%)	The VE was 38% (95% CI: 14 to 55%).	Level II-2	Fair
Studies identified from the update literature search: **Maltezou HC, Stavros S, Asimakopoulos G et al.** Effectiveness of maternal vaccination with quadrivalent inactivated influenza vaccine in	LCI in infants up to 6 months of age.	IIV (Seasonal influenza vaccine)	Cohort studies [46, 49, 50] Countries: Greece Australia Follow up:	Infants up to 6 months of age (n=296,611) Infants born to vaccinated gestational parent:	The MA included 3 cohort studies. The pooled VE was 41% (95% CI: 23 to 55), I^2=17%.	Level II-2	Fair

pregnant women and their infants in 2019-2020. 2022 [46] Funded by Sanofi **Foo D, Sarna M, Pereira G et al.** Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood. 2022 [49] Funded by the National Health and Medical Research Council, Curtin University Graduate Research School, Wesfarmers Centre of Vaccines & Infectious Disease. **Rowe SL, Leder K, Perrett KP, et al.** Maternal Vaccination and Infant Influenza and Pertussis. 2021 [50] Funded by the Victoria State Government Department of Health in Australia as part of routine vaccine program evaluation.			2019-2020 influenza season (n=1) Not restricted to influenza season (n=2) between 2012 and 2017 Funding: Non-industry (n=2) and industry (n=1)	n=100,042 (33.7%) Infants born to unvaccinated gestational parent: n=196,569 (66.3%)			
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN **And studies identified from the update literature search:** **Nunes MC, Walaza S, Meiring S, et al.** Effectiveness of influenza vaccination of pregnant women for prevention	Hospitalization due to LCI infection in infants up to 6 months of age.	IIV (Seasonal influenza vaccine)	TND studies (Benowitz 2010, McRae 2022, and Nunes 2022) [45, 47, 51] Countries: Australia (n=1) South Africa (n=1) United States (n=1) Follow up:	Infants up to 6 months of age (n=1,702). Infants born to vaccinated gestational parent: n=612 (36.0%) Infants born to unvaccinated gestational	The MA included 3 TND studies. The pooled aVE was 42% (95% CI: 16 to 59%), I^2=71%.	Level II-2	Fair

of maternal and early infant influenza-associated hospitalizations in South Africa: A prospective test-negative study. 2022 [47] Funded by the National Institute for Communicable Diseases of the National Health Laboratory Service; the US Centers for Disease Control and Prevention; and the Bill and Melinda Gates Foundation. **McRae J, Blyth CC, Cheng AC et al.** Preventing severe influenza in Australian infants: Maternal influenza vaccine effectiveness in the PAEDS-FluCAN networks using the test-negative design. 2022 [51] Funded by the National Health and Medical Research Council, Australian Government Department of Health, and Departments of Health in NSW, Victoria, Queensland, South Australia, Western Australia, and the Northern Territory.			5 influenza seasons between 2015 to 2019 (n=2) Not restricted to influenza season (n=1) between 2000/10 and 2009/04 Funding: Non-industry (n=3)	parent: n=1,090 (64.0%)			
Foo D, Sarna M, Pereira G et al. Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood. 2022 [49] Funded by the National Health and Medical Research Council, Curtin University Graduate Research School, Wesfarmers	Hospitalization due to LCI in infants up to 6 months of age.	IIV (Seasonal influenza vaccine)	Retrospective, population-based cohort study. Country: Australia Follow up: Not restricted to influenza seasons between 2012/04/01 and 2017/07/01	Singleton, live-born infants (n=124,760) Infants born to vaccinated gestational parent: n=14,396 (11.5%)	The aVE was 62% (95% CI: 9 to 84%).	Level II-2	Good

Centre of Vaccines & Infectious Disease.			Funding: Non-industry	Infants born to unvaccinated gestational parent: n=110,364 (88.5%)			
Rowe SL, Leder K, Perrett KP, et al. Maternal Vaccination and Infant Influenza and Pertussis. 2021 [50] Funded by the Victoria State Government Department of Health in Australia as part of routine vaccine program evaluation.	Hospitalization due to LCI in infants up to 6 months of age.	IIV (Seasonal influenza vaccine)	Retrospective cohort study Country: Australia Follow up: Not restricted to influenza seasons between 2015/09/01 and 2017/12/31 Funding: Non-industry	Infants up to 6 months of age (n=185,404). Infants born to vaccinated gestational parent: n=85,365 (46.0%) Infants born to unvaccinated gestational parent: n=86,012 (46.4%) Infants born to gestational parents with missing/unknown vaccination status: n=14,027 (7.6%)	The aVE was 20.85% (95% CI: -17.74 to 46.79%) in infant under 6 months of age. The aVE was 34.37% (95% CI: -14.83 to 62.49%) in infant under 2 months of age, and the aVE was 4.00% (95% CI: -66.75 to 44.73%) in infants 2 months to under 6 months of age.	Level II-2	Fair
Safety							
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Non-obstetric SAEs in pregnant persons: severe systemic reactions within 7 days of intervention	IIV3 (Vaxigrip®, Sanofi) Placebo Active control: Meningococcal quadrivalent vaccine	2 RCTs [41, 42] Countries: Mali (n=1) South Africa (n=1) Follow up: Not restricted to influenza season	Pregnant individuals (n=4,540) IIV3: n=2,286 (50.3%) Placebo: n=172 (3.8%)	No discernible difference between groups in either included RCT. Tapia et al., 2016: 2 of 2,105 vaccinated and 0	Level I	Fair

		(Menactra®, Sanofi)	(n=2) between 2011 and 2014 Funding: Non-industry (n=2)	Active control: n=2,082 (45.9%)	of 2,082 control [42]. Madhi et al., 2014: 27 of 181 vaccinated and 19 of 172 control (p=0.36) [41].		
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Non-obstetric SAEs in pregnant persons: peripartum hospitalization	IIV3 (Fluarix, GSK) Active control: Pneumococcal vaccine, 23-valent (Pneumovax® 23, Merck)	RCT [43] Country: Bangladesh Follow up: Not restricted to influenza season between 2004/08 and 2005/11 Funding: Mixed funding	Pregnant individuals (n=316) IIV3: n=159 (50.3%) Active control: n=157 (49.7%)	Single RCT found no apparent difference in risk between IIV3 (1 event/159) and active control (2 events/157).	Level I	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Non-obstetric SAEs in pregnant persons: events possibly or probably related to vaccination within 30 days of intervention	IIV3 (Vaxigrip®, Sanofi) Placebo	RCT [41] Country: South Africa Follow up: Enrolled before the 2011-2012 and 2012-2013 influenza seasons Funding: Non-industry	Pregnant individuals (n=2,116) IIV3: n=1,062 (50.2%) Placebo: n=1,054 (49.8%)	Single RCT found no apparent difference in risk between IIV3 (1/1,062) and placebo (0/1,054) groups.	Level I	Good
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during	Non-obstetric SAEs in pregnant persons: events unrelated to	IIV3 (Seasonal influenza vaccine)	Retrospective cohort study [54] Country:	Pregnant persons in the second or third trimester of	A single cohort study found no apparent difference in risk	Level II-2	Good

pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	pregnancy causing hospitalization within 42 days of vaccine administration		United States Follow up: 6 influenza seasons between 1998 and 2003 Funding: Non-industry	gestation (n=1,051) IIV3: n=225 (21.4%) Unvaccinated: n=826 (78.6%)	between IIV3 (2/225) and unvaccinated pregnant individuals (3/826).		
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Non-obstetric SAEs in pregnant persons: inpatient Guillain-Barré syndrome within 42 days	IIV3 (Seasonal influenza vaccine)	Retrospective cohort study [59] Country: United States Follow up: Not restricted to influenza season between 2002/06/01 and 2009/07/31 Funding: Non-industry and insurance	Pregnant persons in the first trimester of gestation (n=223,898) IIV3: n=75,906 (33.9%) Unvaccinated: n=147,992 (66.1%)	A single cohort study found no significant difference between IIV3 vaccinated (0/75,906) and unvaccinated (1/147,992) pregnant persons (p=0.34).	Level II-2	Good
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Non-obstetric SAEs in pregnant persons: no defined and time of follow-up not reported	IIV3 (Seasonal influenza vaccine)	Retrospective cohort study [58] Country: India Follow up: Not restricted to influenza season between 2016/01 and 2018/03 Funding: Not reported	Pregnant persons (n=346) IIV3: n=288 (83.2%) Unvaccinated: n=58 (16.8%)	No events found in a single cohort study of 288 IIV3 vaccinated and 58 unvaccinated pregnant persons.	Level II-2	Fair

Ledlie S, Gandhi-Banga S, Shrestha et al. Exposure to quadrivalent influenza vaccine during pregnancy: Results from a global pregnancy registry. 2022 [60] Funded by Sanofi	Non-obstetric AEs in pregnant persons: Guillain-Barré syndrome	IIV4 (Fluzone® Quadrivalent; Sanofi)	Retrospective and prospective case series, multicenters Countries: United States Canada Australia Brazil Mexico New Zealand Thailand Costa Rica India Follow up: Between 2013/08 and 2019/09 Funding: Industry	Individuals of reproductive age who were exposed to IIV4 during pregnancy or within 30 days of their last menstrual period (n=239) Trimester of exposure, n (%): First: 42 (17.6%) Second: 82 (34.3%) Third: 58 (24.3%) Unknown: 57 (23.9%)	One (0.4%) case of Guillain-Barré syndrome occurred within 5 days of vaccination in a 29-year-old female who recovered and gave birth to a healthy baby while recovering.	Level III	Poor Reporting bias High rate of loss to follow up (80%)
Carreras JJ, Lluch JA, Taboada JA, et al. Adverse events in pregnant women with the tetravalent influenza vaccine obtained from cell cultures. 2022 [56] Funded by Seqirus	Non-obstetric AEs in pregnant persons at any time after vaccine administration.	IIV4-cc (Flucelvax® Quad, Seqirus)	Retrospective cohort study, multicenter Country: Spain Follow up: 2019-2020 influenza season Funding: Industry	Individuals 18 to 64 years old vaccinated with IIV4-cc (n=244,731). Pregnant individuals: N=24,870 (10.2%) Non-pregnant individuals: N=219,861 (89.8%)	The rate of AEs per 100,000 doses administered was 4.0 and 5.9 in pregnant and non-pregnant individuals, respectively. No serious AE were reported among pregnant individuals.	Level II-2	Poor Reporting bias Inconsistency in the quality of data Limited data provided on AE and timing following vaccine administration

Betancourt-Cravioto M, Cervantes-Powell P, Tapia-Conyer R et al. Improved post-marketing safety surveillance of quadrivalent inactivated influenza vaccine in Mexico using a computerized, SMS-based follow-up system. 2022 [55] Funded by Sanofi	Non-obstetric AEs in pregnant persons within 42 days of vaccine administration	IIV4 (Fluzone® Quadrivalent; Sanofi)	Prospective cohort study, multicenter Country: Mexico Follow up: 3 influenza seasons between 2015-2016 and 2017-2018 Funding: Industry	Individuals 6 months and older who received a routine influenza vaccine at study centers (n=2,013) Pregnant individuals: n=18 (0.9%)	One (5.6%) pregnant individual reported a non-serious AE (i.e., AE did not require a medical visit).	Level II-2	Poor Small sample size Reporting bias No information on AE reported, including severity and duration
Vanni T, Thomé BdC, Oliveira MMM, et al. Active pharmacovigilance of the seasonal trivalent influenza vaccine produced by Instituto Butantan: A prospective cohort study of five target groups. 2021 [57] Funded by the Butantan Foundation	Non-obstetric AEs in pregnant persons within 42 days of vaccine administration	IIV3 (Seasonal influenza vaccine)	Prospective cohort study, multicenter Country: Brazil Follow up: 2 influenza seasons between 2017 and 2018 Funding: Non-industry	Individuals 6 months of age and older who received a routine influenza vaccine at study centers (n=942) Pregnant individuals: n=108 (11.5%)	82 (75.9%) pregnant individuals had an AE. 78 (72.2%) pregnant individuals had an adverse reaction (i.e., any AE with a reasonable causal relationship with the vaccine, according to "Uppsala Monitoring Centre" of the World Health OrganizationUMC-WHO). No SAE was reporting in pregnant.	Level II-2	Fair

Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Infant death up to 6 months of age	IIV3 (Seasonal influenza vaccine: Vaxigrip®, Sanofi; n=3, Fluarix, GSK; n=1) Placebo (n=2) Active control: Meningococcal quadrivalent vaccine (n=1, Menactra®, Sanofi) or Pneumococcal vaccine, 23-valent (n=1, Pneumovax® 23, Merck)	4 RCTs (Zaman 2006, Madhi 2014, Tapia 2016, Steinhoff 2017) [40-43] Countries: Bangladesh (n=1) South Africa (n=1) Mali (n=1) Nepal (n=1) Follow up: Not restricted to influenza season between 2004 and 2014 (n=4) Funding: Non-industry (n=3) and mixed funding (n=1)	Infants up to 6 months of age (n=10,115). IIV3: n=5,071 (50.1%) Placebo or active control: n=5,044 (49.9%)	The MA included 4 RCTs. The pooled risk ratio was 1.14 (95% CI: 0.86 to 1.50), I^2= 9.33%.	Level I	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Infant death up to 6 months of age	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [61] Country: Japan Follow up: Not restricted to influenza season between 2010/11 and 2011/04 Funding: Not reported	Infants diagnosed with fever (n=83). Infants born to vaccinated gestational parent: n=36 (43.4%) Infants born to unvaccinated gestational parent: n=47 (56.6%)	No Infant death was reported among infants born to vaccinated and unvaccinated gestational parent.	Level II-2	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18]	Spontaneous abortion (<20 gestational weeks)	IIV (Seasonal influenza vaccine)	2 cohort studies [62, 63] Countries: Australia (n=1) Canada (n=1)	Pregnant persons (n=1,900).	The MA included 2 cohort studies. The pooled aHR was 0.77 (95%	Level II-2	Good

Funded by the CIHR and the DSEN			United States (n=1) Follow up: Not restricted to influenza season between 2010 and 2017 Funding: No funding (n=1) and mixed funding (n=1)	II V: n=983 (51.7%) Unvaccinated: n=917 (48.3%)	CI: 0.31 to 1.89), I^2=37.51%.		
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Spontaneous abortion (<22 gestational weeks)	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [64] Country: Japan Follow up: Not restricted to the influenza season between 2013/10 and 2013/12. Funding: Non-industry	Individuals in their first trimester of pregnancy (n=2,826) IIV3: n=1,121 (39.7%) Unvaccinated: n=1,705 (60.3%)	A single cohort study reported raw data with the same risk in both exposed and unexposed groups (0.4% and 0.4%, respectively).	Level II-2	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Spontaneous abortion (<20 gestational weeks) within 28 days of vaccine administration	IIV3 (Seasonal influenza vaccine)	Retrospective case-control study) [65] Country: United States Follow up: 2 influenza seasons between 2010/2011 and 2011/2012 Funding: Non-industry	Pregnant individuals between 18- and 44-year-old vaccinated against influenza (n=970).	The aOR was 3.70 (95% CI: 1.40 to 9.40) in 2010/2011 and 1.40 (95% CI: 0.60 to 3.30) in 2011/2012. Post-hoc analyses of 2010/2011 data: Among individuals previously vaccinated with pH1N1-containing vaccine the aOR	Level II-2	Good

					was 7.7 (95% CI: 2.2 to 27.3). Among individuals not vaccinated in the previous season the aOR was 1.3 (95% CI: 0.7 to 2.7).		
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Spontaneous abortion (<20 gestational weeks) within 28 days of vaccine administration	IIV3 (Seasonal influenza vaccine)	Retrospective case-control study [65] Country: United States Follow up: 3 influenza seasons between 2012/2013 and 2014/2015 Funding: Non-industry	Pregnant individuals between 18- and 44-year-old (n=2,472). Vaccinated in the previous season: n=1,254 (50.3%) Not vaccinated in the previous season: n=1,218 (49.3%)	Overall, the aOR was 0.80 (95% CI: 0.60 to 1.10). The aOR was 0.9 (95% CI: 0.6 to 1.5) in those vaccinated in the previous season and 0.7 (95% CI: 0.4 to 1.1) in those not vaccinated in the previous season.	Level II-2	Good
Romano CJ, Hall C, Khodr ZG, et al. History of pandemic H1N1-containing influenza vaccination and risk of spontaneous abortion and birth defects. 2021 [66] Funded by the Defense Health Agency Immunization Healthcare Division and the U.S. Navy Bureau of Medicine and Surgery	Spontaneous abortion (<22 gestational weeks) within 28 days of vaccine administration	IIV3 (Seasonal influenza vaccine)	Retrospective cohort study Country: United States Follow up: 6 influenza seasons between 2008/2009 and 2013/2014 Funding: Non-industry	Pregnant individuals 17 years and older (n=26,264) Exposed to a pH1N1-containing vaccine in the season prior to pregnancy: n=21,736 (82.8%)	The aHR was 1.19 (95% CI: 0.97 to 1.46).	Level II-2	Good

				Exposed to non-pH1N1-containing vaccine in the season prior to pregnancy: n=4,528 (17.2%)			
Robinson C, Oberye J, Van Boxmeer J et al. A prospective cohort study on pregnancy outcomes of persons immunized with a seasonal quadrivalent inactivated influenza vaccine during pregnancy. 2022 [68] Funded by Seqirus Inc.	Spontaneous abortion (<20 gestational weeks).	IIV4 (Afluria® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4 at any time during pregnancy (n=483) Trimester of exposure: First: n=171 (35.4%) second: n=201 (41.6%) third: n=111 (23.0%) Vaccinated <20 gestational weeks: n=160 (33.1%)	4 events (2.5%, 95% CI: 0.7 to 6.3%) were reported among those vaccinated at under 20 gestational weeks (n=160).	Level III	Fair
Robinson C, Van Boxmeer J, Tilson H, et al. Outcomes in pregnant persons immunized with a cell-based quadrivalent inactivated influenza vaccine: A prospective observational cohort study. 2022 [69] Funded by Seqirus Inc.	Spontaneous abortion (<20 gestational weeks).	IIV4-cc (Flucelvax® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding:	Individuals vaccinated with IIV4-cc at any time during pregnancy (n=665) Trimester of exposure: First: n=178 (26.8%) Second: n=277 (41.6%)	4 events (1.9%, 95% CI: 0.5 to 4.8%) were reported among those vaccinated at under 20 gestational weeks (n=211).	Level III	Fair

			Industry	Third: n=210 (31.6%) Vaccinated <20 gestational weeks: n=211 (31.7%)			
Ledlie S, Gandhi-Banga S, Shrestha et al. Exposure to quadrivalent influenza vaccine during pregnancy: Results from a global pregnancy registry. 2022 [60] Funded by Sanofi	Spontaneous abortion	IIV4 (Fluzone® Quadrivalent; Sanofi)	Retrospective and prospective case series, multicenters Countries: United States Canada Australia Brazil Mexico New Zealand Thailand Costa Rica India Follow up: Between 2013/08 and 2019/09 Funding: Industry	Individuals of reproductive age who were exposed to IIV4 during pregnancy or within 30 days of their last menstrual period (n=239) Trimester of exposure, n (%): First: 42 (17.6%) Second: 82 (34.3%) Third: 58 (24.3%) Unknown: 57 (23.9%)	4 events (6.4%, 95% CI: 2.08 to 15.90%) were reported.	Level III	Poor Reporting bias High rate of loss to follow up (80%)
Nwoji U. Seasonal influenza vaccine exposure in pregnancy: 5-year results from a pregnancy registry. 2022 [67] Funded by GlaxoSmithKline Biologicals SA.	Spontaneous abortion (<22 gestational weeks)	IIV3 (Fluarix and FluLaval, GSK) or IIV4 (Fluarix Quadrivalent and FluLaval Quadrivalent, GSK)	Prospective cohort study Country: United States Follow up: Not restricted to influenza seasons between 2014/06/01 to 2019/05/31 Funding:	Individuals vaccinated during pregnancy or within 28 days preceding conception (n=507) Trimester of exposure, n (%): First: n=84 (16.6%)	3 events (2.6%) were reported. 2 occurred among those vaccinated during the first trimester of pregnancy and one had unknown trimester of exposure.	Level III	Poor Reporting bias High rate of loss to follow up (70.8%)

			Industry	Second: n=113 (22.3%) Third: n=91 (17.9%) Unknown: n=219 (43.2%) Lost to follow up: n=359 (70.8%)			
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV3 (Seasonal influenza vaccine)	Retrospective cohort study [83] Country: Australia Follow up: Not restricted to influenza season between 2012/04/01 and 2013/12/31 Funding: Non-industry	Pregnant individuals (n=58,008) IIV3: n= 5,076 (8.8%) Unvaccinated: n= 52,932 (91.2%)	The aHR was 0.49 (95% CI: 0.29 to 0.83).	Level II-2	Good
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV (Seasonal influenza vaccine)	Retrospective case-control study [96] Country: United States Follow up: Not restricted to influenza season between 2012/01/01 and 2015/09/30 Founding: Non-industry	Pregnant persons (n=12,109) II V: n=1,736 (14.3%) Unvaccinated: n=10,373 (85.7%)	The aOR was 0.95 (95% CI: 0.79 to 1.14).	Level II-2	Good

Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV (Seasonal influenza vaccine)	Retrospective cohort study [97] Country: Australia Follow up: Between December and July, from 2012/04 and 2015/07 Funding: Non-industry	Individuals in their first trimester of pregnancy (n=11,955) IIV: n=2,391 (20.0%) Unvaccinated: n=9,564 (80.0%)	The adjusted risk ratio (aRR) was 1.18 (95% CI: 0.64 to 2.18).	Level II-2	Good
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV (Seasonal influenza vaccine)	Prospective cohort study [62] Countries: Canada United States Follow up: Not restricted to influenza season between 2010 and 2014 Funding: Mixed funding	Pregnant individuals (n=1,707) IIV: n=1,240 (72.6%) First trimester: n=477 (27.9%) Unvaccinated: n=467 (27.4%) First trimester: n=467 (27.4%)	The risk ratio was 0.38 (95% CI: 0.05 to 2.92). In analysis restricting to vaccination during the first trimester of pregnancy, the risk ratio was 0.98 (95% CI: 0.13 to 7.50).	Level II-2	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [84] Country: United States Follow up: Between October and March from 2003 to 2008 Funding: Not reported	Pregnant persons (n=85,783) IIV3: n=8,864 (10.3%) First trimester: n=447 (0.5%) Unvaccinated: n=76,919 (89.7%)	The risk ratio was 0.60 (95% CI: 0.41 to 86). In analysis restricting to vaccination during the first trimester of pregnancy, the risk ratio was 2.54 (95% CI: 0.36 to 18.01).	Level II-2	Good

				First trimester: n=76,919 (89.7%)			
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [64] Country: Japan Follow up: Between September and December 2013 Funding: Non-industry	Pregnant individuals (n=10,330) IIV3: n=3,943 (38.2%) First trimester: n=1,121 (10.9%) Unvaccinated: n=6,387 (61.8%) First trimester: n=1,705 (16.5%)	The risk ratio was 0.44 (95% CI: 0.12 to 1.58). In analysis restricting to the first trimester of pregnancy, the risk ratio was 0.30 (95% CI: 0.01 to 6.33).	Level II-2	Fair
Giles ML, Davey MA, Wallace EM. Associations Between Maternal Immunisation and Reduced Rates of Preterm Birth and Stillbirth: A Population Based Retrospective Cohort Study. Frontiers in Immunology. 2021 [85] Funding: Not reported	Stillbirth	IIV (Seasonal influenza vaccine)	Retrospective cohort study Country: Australia Follow up: Not restricted to influenza season between 2015/07 and 2018/12 Funding: Not reported	Pregnant persons with singleton pregnancies >28 gestational weeks (n=269,493) IIV: n=138,698 (51.5%) Unvaccinated: n=112,155 (41.6%) Not reported/unknown: n=18,640 (6.9%)	The aRR was 0.25 (95% CI: 0.20 to 0.31).	Level II-2	Fair

Robinson C, Oberye J, van Boxmeer J, et al. A Prospective Cohort Study on Pregnancy Outcomes of Persons Immunized with a Seasonal Quadrivalent Inactivated Influenza Vaccine during Pregnancy. Vaccines. 2022. [68] Funded by Seqirus Inc.	Stillbirth (≥20 gestational weeks or ≥500g)	IIV4 (Afluria® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4 at any time during pregnancy (n=483) Trimester of exposure: First: n=171 (35.4%) Second: n=201 (41.6%) Third: n=111 (23.0%)	2 (0.4%, 95% CI: 0.1 to 1.5%) events were reported. One occurred in an individual vaccinated during the first trimester and one in an individual vaccinated during the second trimester of pregnancy.	Level III	Fair
Robinson C, Van Boxmeer J, Tilson H, et al. Outcomes in Pregnant Persons Immunized with a Cell-Based Quadrivalent Inactivated Influenza Vaccine: A Prospective Observational Cohort Study. Vaccines. 2022. [69] Funded by Seqirus Inc.	Stillbirth (≥20 gestational weeks or ≥500g)	IIV4-cc (Flucelvax® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4-cc at any time during pregnancy (n=665) Trimester of exposure: First: n=178 (26.8%) Second: n=277 (41.6%) Third: n=210 (31.6%)	No event was reported.	Level III	Fair
Nwoji U. Seasonal influenza vaccine exposure in pregnancy: 5-year results from a pregnancy registry. Hum Vaccin Immunother. 2022. [67] Funded by GlaxoSmithKline Biologicals SA	Stillbirth (≥18-22 gestational weeks or ≥500g)	IIV3 (Fluarix and FluLaval, GSK) or IIV4 (Fluarix Quadrivalent and FluLaval Quadrivalent, GSK)	Prospective cohort study Country: United States Follow up: Not restricted to influenza seasons between 2014/06/01 to 2019/05/31	Individuals vaccinated during pregnancy or within 28 days preceding conception (n=507) Trimester of exposure, n (%):	One (0.9%) event was reported among an individual vaccinated during the first trimester of pregnancy. Causal association with vaccination was	Level III	Poor Reporting bias High rate of loss to follow up (70.8%)

			Funding: Industry	First: n=84 (16.6%) Second: n=113 (22.3%) Third: n=91 (17.9%) Unknown: n=219 (43.2%) Lost to follow up: n=359 (70.8%)	ruled out.		
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Pre-term birth (<37 completed gestational weeks)	IIV3 (Seasonal influenza vaccine)	Fifteen cohort studies Countries: Australia (n=2) Canada (n=4) Laos (n=1) Nicaragua (n=1) United States (n=8) Follow up: 6 studies were restricted to influenza seasons between 2004 and 2015 9 studies were not restricted to influenza seasons between 2002 and 2018 Funding: Non-industry (n=10), non-industry and insurance (n=2), mixed (n=1), no funding (n=1), and not reported (n=1).	Studies that accounted for immortal time bias (n=152,476) IIV3: n=66,749 (43.8%) Unvaccinated: n=85,727 (56.2%) Studies that did not account for immortal time bias (n=151,032) IIV3: n=67,558 (44.7%) Unvaccinated: n=83,474 (55.3%) When influenza vaccination	The MA included 6 cohort studies that accounted for immortal time bias. The pooled aHR was 1.09 (95% CI: 0.89 to 1.33), I^2=28.18% for studies that accounted for immortal time bias. The MA included ten cohort studies that did not account for immortal time bias. The pooled aRR was 0.86 (95% CI: 0.76 to 0.97), I^2=71.15% for studies that did not account for	Level II-2	Good

				during the first trimester of pregnancy was considered (n=47,211) IIV3: n=19,135 (40.5%) Unvaccinated: n=28,076 (59.5%)	immortal time bias. A MA included six cohort studies restricted to vaccination during the first trimester of pregnancy. The pooled aHR was 1.05 (95% CI: 0.92 to 1.20), I^2=30.46% for studies restricted to vaccination during the first trimester of pregnancy.		
Duque J, Howe AS, Azziz-Baumgartner et al. Multi-decade national cohort identifies adverse pregnancy and birth outcomes associated with acute respiratory illness hospitalisations during the influenza season. 2022 [87] Funding: not reported	Preterm birth (<37 weeks of gestation)	IIV (Seasonal influenza vaccine)	Retrospective cohort Country: New Zealand Follow up: Sixteen influenza seasons between 2003 and 2018 Funding: Not reported	Individuals between 15 and 49 years of age who were pregnant (n=822,391) Vaccinated pregnant persons with preterm birth between 2010 and 2018: n=3,895 (6.1%) Unvaccinated pregnant persons with preterm birth between 2010 and 2018:	The aHR was 0.79 (95% CI: 0.77 to 0.82).	Level II-2	Good

				n=29,825 (8.0%)			
Giles ML, Davey M and Wallace EM. Associations between maternal immunisation and reduced rates of preterm birth and stillbirth: A population based retrospective cohort study. 2021 [85] Funding not reported	Preterm birth (<37 weeks of gestation)	IIV (Seasonal influenza vaccine)	Retrospective cohort study Country: Australia Follow up: Not restricted to influenza season between 2015/07 and 2018/12 Funding: Not reported	Pregnant persons with singleton pregnancies >28 gestational weeks (n=269,493) IIV: n=138,698 (51.5%) Unvaccinated: n=112,155 (41.6%) Not reported/unknown: n=18,640 (6.9%)	The aRR was 0.69 (95% CI: 0.66 to 0.72).	Level II-2	Fair
Robinson C, Oberye J, van Boxmeer J, et al. A Prospective Cohort Study on Pregnancy Outcomes of Persons Immunized with a Seasonal Quadrivalent Inactivated Influenza Vaccine during Pregnancy. Vaccines. 2022. [68] Funded by Seqirus Inc.	Preterm birth (<37 weeks of gestation)	IIV4 (Afluria® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4 at any time during pregnancy (n=483) Trimester of exposure: First: n=171 (35.4%) Second: n=201 (41.6%) Third: n=111 (23.0%)	Overall, 31 (7.2%) events were reported. Events by trimester of exposure, n (%): First: n=10 (6.6%) Second: n=17 (8.9%) Third: n=4 (4.7%)	Level III	Fair
Robinson C, Van Boxmeer J, Tilson H, et al. Outcomes in Pregnant Persons Immunized with a Cell-Based Quadrivalent Inactivated Influenza Vaccine: A Prospective Observational	Preterm birth (<37 weeks of gestation)	IIV4-cc (Flucelvax® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States	Individuals vaccinated with IIV4-cc at any time during pregnancy (n=665)	Overall, 52 (9.2%) events were reported. Events by trimester of exposure, n (%):	Level III	Fair

Cohort Study. Vaccines. 2022. (69) Funded by Seqirus Inc.			Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Trimester of exposure: First: n=178 (26.8%) Second: n=277 (41.6%) Third: n=210 (31.6%)	First: n=17 (10.3%) Second: n=27 (10.8%) Third: n=8 (5.4%)		
Ledlie S, Gandhi-Banga S, Shrestha et al. Exposure to quadrivalent influenza vaccine during pregnancy: Results from a global pregnancy registry. 2022 (60) Funded by Sanofi	Preterm birth (<37 weeks of gestation)	IIV4 (Fluzone® Quadrivalent; Sanofi)	Retrospective and prospective case series, multicenters Countries: United States Canada Australia Brazil Mexico New Zealand Thailand Costa Rica India Follow up: Between 2013/08 and 2019/09 Funding: Industry	Individuals of reproductive age who were exposed to IIV4 during pregnancy or within 30 days of their last menstrual period (n=239) Trimester of exposure, n (%): First: 42 (17.6%) Second: 82 (34.3%) Third: 58 (24.3%) Unknown: 57 (23.9%)	One (6.67%) event was reported among reports with known neonatal outcomes (n=15).	Level III	Poor Reporting bias High rate of loss to follow up (80%)
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. (18) Funded by the CIHR and the DSEN **And study identified in update literature search:**	Small-for-gestational-age birth	IIV (Seasonal influenza vaccine)	12 cohort studies Countries: Canada (n=2) United States (n=6) Australia (n=2) Nicaragua (n=1) Laos (n=1) Follow up: Restricted to influenza season between 2014 and 2015 (n=2)	Pregnant persons (n=548,277) IIV: n=271,045 (n=49.4%) Unvaccinated: n=277,232 (50.6%)	The MA included 12 cohort studies. The pooled aRR was 0.97 (95% CI: 0.90 to 1.04), I^2=71%.	Level II-2	Fair

Giles ML, Davey M and Wallace EM. Associations between maternal immunisation and reduced rates of preterm birth and stillbirth: A population based retrospective cohort study. 2021 [85] Funding not reported			Not restricted to influenza season between 2004 and 2017 (n=10) Funding: Non-industry (n=6), non-industry and insurance (n=2), mixed funding (n=1), not reported (n=2), and no funding (n=1).				
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN **And study identified in update literature search:** **Duque J, Howe AS, Azziz-Baumgartner et al.** Multi-decade national cohort identifies adverse pregnancy and birth outcomes associated with acute respiratory illness hospitalisations during the influenza season. 2022 [87] Funding not reported	Low birth weight (<2,500 g)	IIV (Seasonal influenza vaccine)	3 cohort studies [63, 86, 87] Countries: New Zealand (n=1) Australia (n=1) United States (n=1) Follow up: Sixteen influenza seasons between 2003 and 2018 (n=1) Not restricted to influenza season between 2010 and 2015 (n=2) Funding: Non-industry (n=1), no funding (n=1), and not reported (n=1)	Pregnant persons (n=168,633) IIV: n=68,039 (40.3%) Unvaccinated: n=100,594 (59.7%)	The MA included 3 cohort studies. The pooled aHR was 0.89 (95% CI: 0.83 to 0.96), I^2=37%.	Level II-2	Good
Robinson C, Oberye J, van Boxmeer J, et al. A Prospective Cohort Study on Pregnancy Outcomes of Persons Immunized with a Seasonal Quadrivalent	Low birth weight (<2,500 g)	IIV4 (Afluria® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States	Individuals vaccinated with IIV4 at any time during pregnancy (n=483)	Overall, 25 (5.4%) events occurred. Events by trimester of	Level III	Fair

Inactivated Influenza Vaccine during Pregnancy. Vaccines. 2022. [68] Funded by Seqirus Inc.			Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Trimester of exposure: First: n=171 (35.4%) Second: n=201 (41.6%) Third: n=111 (23.0%)	exposure, n (%): First: n=7 (4.4%) Second: n=13 (6.7%) Third: n=5 (4.5%)		
Robinson C, Van Boxmeer J, Tilson H, et al. Outcomes in Pregnant Persons Immunized with a Cell-Based Quadrivalent Inactivated Influenza Vaccine: A Prospective Observational Cohort Study. Vaccines. 2022. [69] Funded by Seqirus Inc.	Low birth weight (<2,500 g)	IIV4-cc (Flucelvax® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4-cc at any time during pregnancy (n=665) Trimester of exposure: First: n=178 (26.8%) Second: n=277 (41.6%) Third: n=210 (31.6%)	Overall, 37 (5.8%) events occurred. Events by trimester of exposure, n (%): First: n=14 (8.3%) Second: n=15 (5.7%) Third: n=8 (3.9%)	Level III	Fair
Ledlie S, Gandhi-Banga S, Shrestha et al. Exposure to quadrivalent influenza vaccine during pregnancy: Results from a global pregnancy registry. 2022 [60] Funded by Sanofi	Low birth weight (<2,500 g)	IIV4 (Fluzone® Quadrivalent; Sanofi)	Retrospective and prospective case series, multicenters Countries: United States Canada Australia Brazil Mexico New Zealand Thailand Costa Rica India Follow up: Not restricted to influenza seasons between 2013/08 and 2019/09	Individuals of reproductive age who were exposed to IIV4 during pregnancy or within 30 days of their last menstrual period (n=239). Trimester of exposure, n (%): First: 42 (17.6%) Second: 82 (34.3%) Third: 58 (24.3%)	2 (10.0%) events were reported among reports with known neonatal outcomes (n=30).	Level III	Poor Reporting bias High rate of loss to follow up (80%)

			Funding: Industry	Unknown: 57 (23.9%)			
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Congenital anomalies identified at birth	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [63] Country: Australia Follow up: Not restricted to influenza season between 2015/03 and 2017/12 Funding: No funding	Pregnant persons (n=1,207). IIV3 during the first trimester of pregnancy: n=141 (11.7%) Unvaccinated: n=1,066 (88.3%)	The aRR was 0.33 (95% CI: 0.04 to 2.73).	Level II-2	Good
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Congenital anomalies identified at birth	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [84] Country: United States Follow up: Not restricted to influenza season between October to March from 2003 to 2008 Funding: Not reported	Pregnant persons (n=77,366). IIV3 during the first trimester of pregnancy: n=447 (0.6%) Unvaccinated during the first trimester of pregnancy: n=76,919 (99.4)	The OR was 0.67 (95% CI: 0.36 to 1.25).	Level II-2	Fair
Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18]	Congenital anomalies identified at birth	IIV3 (Seasonal influenza vaccine)	Prospective cohort study [64] Country: Japan Follow up:	Pregnant persons (n=2,826). IIV3 during the first trimester of pregnancy:	Single cohort study reported no significant difference between infants born to gestational	Level II-2	Fair

Funded by the CIHR and the DSEN			Not restricted to influenza season between September and December 2013 Funding: Non-industry	n=1,121 (39.7%) Unvaccinated: n=1,705 (60.3%)	parent vaccinated with IIV3 in the first trimester (33/1,121) and unvaccinated gestational parents (55/1,705); p=0.67.		
Robinson C, Oberye J, van Boxmeer J, et al. A Prospective Cohort Study on Pregnancy Outcomes of Persons Immunized with a Seasonal Quadrivalent Inactivated Influenza Vaccine during Pregnancy. Vaccines. 2022. [68] Funded by Seqirus Inc.	Congenital anomalies identified at birth	IIV4 (Afluria® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4 at any time during pregnancy (n=483). Trimester of exposure: First: n=171 (35.4%) second: n=201 (41.6%) third: n=111 (23.0%)	2 (1.2%) cases of major congenital malformation were identified among infant born to parent that received IIV4 vaccine during the first trimester of pregnancy.	Level III	Fair
Robinson C, Van Boxmeer J, Tilson H, et al. Outcomes in Pregnant Persons Immunized with a Cell-Based Quadrivalent Inactivated Influenza Vaccine: A Prospective Observational Cohort Study. Vaccines. 2022. [18] Funded by Seqirus Inc.	Congenital anomalies identified at birth	IIV4-cc (Flucelvax® Quadrivalent, Seqirus)	Single-arm prospective cohort study Country: United States Follow up: 4 influenza seasons between 2017/2018 and 2020/2021 Funding: Industry	Individuals vaccinated with IIV4-cc at any time during pregnancy (n=665). Trimester of exposure: First: n=178 (26.8%) Second: n=277 (41.6%) Third: n=210 (31.6%)	One live-born infant (0.6%) with major congenital malformation was born to an individual that received IIV4-cc during the first trimester of pregnancy and the reported birth defect had a known cause other than exposure to the study vaccine.	Level III	Fair

Wolfe D, Garritty C, Hamel C, et al. Safety and effectiveness of influenza vaccine during pregnancy – a systematic review. 2022. [18] Funded by the CIHR and the DSEN	Congenital anomalies identified from birth up to 6 months of age	IIV (Seasonal influenza vaccine)	Retrospective case-control study [98] Country: United States Follow up: 3 influenza seasons from 2011/2012 to 2013/2014 Funding: Mixed funding	Pregnant persons (n=4,277). IIV during the first trimester of pregnancy: n=711 (16.6%) Unvaccinated: n=3,566 (83.4%)	The aOR was 1.01 (95% CI: 0.85 to 1.21).	Level II-2	Fair
Romano CJ, Hall C, Khodr ZG, et al. History of pandemic H1N1-containing influenza vaccination and risk of spontaneous abortion and birth defects. 2021 [66] Funding: Defense Health Agency Immunization Healthcare Division and the U.S. Navy Bureau of Medicine and Surgery	Congenital anomalies identified from birth up to 6 months of age	IIV3 (Seasonal influenza vaccine)	Retrospective cohort study Country: United States Follow up: 6 influenza seasons between 2008/2009 and 2013/2014 Funding: Non-industry	Pregnant individuals 17 years and older (n=26,264) Exposed to a pH1N1-containing vaccine in the season prior to pregnancy: n=21,736 (82.8%) Exposed to non-pH1N1-containing vaccine in the season prior to pregnancy: n=4,528 (17.2%)	The aHR was 1.05 (95% CI: 0.83 to 1.34).	Level II-2	Good
Sarna M, Pereira GF, Foo D et al. The risk of major structural birth defects associated with seasonal influenza vaccination	Congenital anomalies identified from birth up to 6 months of age	IIV (Seasonal influenza vaccine)	Retrospective cohort study Country: Australia	Pregnant persons (113,936)	Weighted prevalence ratio up to one month of birth was 0.98	Level II-2	Good

during pregnancy: a population-based cohort study [99] Funded by Curtin University of Technology; National Health and Medical Research Council; Norges Forskningsrad; Telethon Kids Institute, Department of Health			Follow up: Not restricted to influenza season between 2012/04/01 and 2016/04/12 Funding: Non-industry	IIV during the first trimester of pregnancy: n=2,811 (2.5%) Unvaccinated: n=111,125 (97.5%)	(95% CI: 0.68 to 1.43).		
Nwoji U. Seasonal influenza vaccine exposure in pregnancy: 5-year results from a pregnancy registry. Hum Vaccin Immunother. 2022. [67] Funded by GlaxoSmithKline Biologicals SA	Congenital anomalies identified from birth up to 6 months of age	IIV3 (Fluarix and FluLaval, GSK) or IIV4 (Fluarix Quadrivalent and FluLaval Quadrivalent, GSK)	Prospective cohort study Country: United States Follow up: Not restricted to influenza seasons between 2014/06/01 to 2019/05/31 Funding: Industry	Individuals vaccinated during pregnancy or within 28 days preceding conception (n=507) Trimester of exposure, n (%): First: n=84 (16.6%) Second: n=113 (22.3%) Third: n=91 (17.9%) Unknown: n=219 (43.2%) Lost to follow up: n=359 (70.8%)	Among those with known pregnancy outcome (n=115), 3 (2.6%) events were deemed unlikely to be causally associated with IIV and one (0.9%) event had insufficient information to assess causality.	Level III	Poor Reporting bias High rate of loss to follow up (70.8%)
Ledlie S, Gandhi-Banga S, Shrestha et al. Exposure to quadrivalent influenza vaccine during pregnancy: Results from a global pregnancy registry. 2022 [60] Funded by Sanofi	Congenital anomalies identified from birth up to 6 months of age	IIV4 (Fluzone® Quadrivalent; Sanofi)	Retrospective and prospective case series, multicenters Countries: United States Canada	Individuals of reproductive age who were exposed to IIV4 during pregnancy or within 30 days	One event was reported among those vaccinated during the first trimester of pregnancy with	Level III	Poor Reporting bias High rate of loss to

			Australia Brazil Mexico New Zealand Thailand Costa Rica India Follow up: Between 2013/08 and 2019/09 Funding: Industry	of their last menstrual period (n=239) Trimester of exposure, n (%): First: 42 (17.6%) Second: 82 (34.3%) Third: 58 (24.3%) Unknown: 57 (23.9%)	known neonatal outcomes.		follow up (80%)

Abbreviation: AE; adverse event, aHR; adjusted hazard ratio, aOR; adjusted odds ratio, aRR; adjusted risk ratio, aVE; adjusted vaccine effectiveness, CI; confidence interval, CIHR; Canadian Institutes of Health Research, DSEN; Drug Safety and Effectiveness Network, GSK; GlaxoSmithKline; IIV; inactivated influenza vaccine, IIV3; trivalent inactivated influenza vaccine, IIV4; quadrivalent inactivated influenza vaccine, IIV4-cc; Cell-culture based quadrivalent inactivated influenza vaccine, MA; meta-analysis, pH1N1; pandemic A(H1N1) strain, RCT; randomized controlled trial, RT-PCR; reverse transcription polymerase chain reaction, TND; test-negative design, VE; vaccine effectiveness; GSK: GlaxoSmithKline; NA: not applicable

Table 2. Ranking individual studies: Levels of evidence based on research design

Level	Description
I	A randomized controlled trial.
II-1	A controlled trial without randomization.
II-2	A cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	A multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Clinical experience, descriptive study or case report, or report of expert committees.

Table 3. Ranking individual studies: Quality (internal validity) rating of evidence

Quality rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific[a] "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

[a] General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Table 4. NACI recommendations: Strength of recommendation

	Strong	Discretionary
Wording	“should/should not be offered”	“may/may not be offered”
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), or Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, or uncertainty in the evidence of advantages and disadvantages exists
Implications	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 offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

XI. LIST OF ABBREVIATIONS

AE	Adverse event
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
aVE	Adjusted vaccine effectiveness
CI	Confidence interval
CIG	Canadian Immunization Guide
CIHR	Canadian Institutes of Health Research
CNICS	Childhood National Immunization Coverage Survey
DSEN	Drug Safety and Effectiveness Network
EEFA	Ethics, equity, feasibility, and acceptability
FDA	Food and Drug Administration (United States)
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	Hemagglutinin
HI	Hemagglutination inhibition
HR	Hazard ratio
ICU	Intensive care unit
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IIV4-cc	Cell-culture based quadrivalent inactivated influenza vaccine
IIV4-SD	Standard-dose quadrivalent inactivated influenza vaccine
IIV-Adj	Adjuvanted inactivated influenza vaccine
IIV-HD	High-dose inactivated influenza vaccine

IIV-SD	Standard-dose inactivated influenza vaccine
ILI	Influenza-like illness
IM	Intramuscular
IRR	Incidence rate ratio
IWG	Influenza Working Group
LAIV	Live attenuated influenza vaccine (egg based)
LBW	Low birthweight
LCI	Laboratory-confirmed influenza
MA	Meta-analysis
NA	Neuraminidase
NACI	National Advisory Committee on Immunization
NOC	Notice of Compliance
NOS	Newcastle Ottawa Scale
OR	Odds ratio
PHAC	Public Health Agency of Canada
RCT	Randomized controlled trial
RIV	Recombinant influenza vaccine
RIV4	Quadrivalent recombinant influenza vaccine
RoB	Risk of bias
RR	Risk ratio
RT-PCR	Reverse transcription polymerase chain reaction
rVE	Relative vaccine efficacy
SAB	Spontaneous abortion
SAE	Serious Adverse Event
SGA	Small for Gestational Age
SR	Systematic Review

SVP	Canadian Survey on Vaccination During Pregnancy Study
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
US	United States
VAERS	Vaccine Adverse Event Reporting System (US)
VE	Vaccine effectiveness
WHO	World Health Organization

XII. ACKNOWLEDGEMENTS

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APPENDIX A. REVIEW UPDATE METHODS

The methods related to the review update completed by the NACI Secretariat were generally aligned with those used by Wolfe et al. (2020) [18].

Review Questions

The following research questions were addressed:

Research question #1: Are influenza vaccines safe for pregnant persons and their newborn infants if received any time during pregnancy?

Research question #2: Are influenza vaccines effective for preventing influenza and its complications for pregnant persons and their newborn infants if received at any time during pregnancy?

Study Eligibility Criteria

Eligibility criteria defining studies for inclusions were the same as those used by Wolfe et al. (2020) apart from the inclusion of single-arm cohort studies and studies based on databases of voluntary reporting or surveillance of AEs (Table 5) [18]. These studies were included in the review update completed by the NACI Secretariat to capture evidence on more recently licensed influenza vaccines that are based upon new different technologies, including quadrivalent mammalian cell culture-based vaccines and RIV.

Table 5. Study Eligibility Criteria

	Inclusion criteria	**Exclusion criteria**
Population	Pregnant women and their unborn and newborn infants under 6 months of age	Women vaccinated preconception or post-partum
Interventions	Seasonal and pandemic influenza vaccines of any valency that were indicated for adults	Vaccines contraindicated during pregnancy (e.g., live-attenuated vaccines)
Comparators	Placebo, no influenza vaccine, active comparators (e.g., other influenza vaccine, meningococcal or pneumococcal vaccines)	No comparator or vaccines contraindicated during pregnancy
Outcomes	Dichotomous measures of the following outcomes: **Maternal** • Vaccine effectiveness against lab-confirmed influenza (LCI) • LCI hospitalization • Influenza-like illness (ILI) and other influenza-associated outcomes	• Immunogenicity outcomes • Outcomes with continuous measures

	• Serious non-obstetric adverse events (SAEs) **Infant** • Vaccine effectiveness against lab-confirmed influenza (LCI) • LCI hospitalization • Influenza-like illness (ILI) and other influenza-associated outcomes • Early neonatal death within 7 days of birth • Death within 6 months of birth **Birth outcomes** • Spontaneous abortion (SAB) • Stillbirth • Preterm birth (PTB) • Small-for-gestational-age birth (SGA) • Low birth weight (LBW) • Congenital anomalies	
Study designs	RCTs, prospective and retrospective cohort studies, case-control and test-negative studies, nested designs, single-arm cohort studies, studies based on databases of voluntary reporting or surveillance of adverse events	Systematic reviews, narrative reviews, case reports, abstracts
Language	English and French language publications only	Other languages

Literature Search

The updated search strategy was developed in collaboration with librarian from the Health Library of Health Canada and PHAC (search strategy available upon request). Separate strategies were performed for RCTs and observational studies. The RCT search was performed in Ovid MEDLINE® ALL, Embase, and the Cochrane Central Register of Controlled Trials. The observational studies were identified using Ovid MEDLINE® ALL and Embase. All searches were performed on January 13, 2023. Searches were restricted to articles published in English and French. Articles retrieved in the Health Library of Health Canada and PHAC literature searches were loaded into RefWorks (ProQuest LLC, Ann Arbor, MI), and uploaded to DistillerSR (Evidence Partners, Ottawa, Canada).

Study Selection Process

Two (2) reviewers independently screened titles and abstracts for study eligibility. The full texts of studies identified in the first phase of screening were assessed independently by 2 reviewers for inclusion in the SR. Screening conflicts were resolved by discussion or arbitration by a third reviewer.

Data Extraction

A data extraction form was developed for this SR. The extraction process was piloted independently by 2 reviewers to assess quality and consistency of data collection. Data were extracted by one reviewer and verified by a second. Study authors were contacted by email to obtain additional data or confirm data when necessary.

The following data were extracted from each report: study design, population characteristics definition of intervention and comparator, outcome definition, statistical analyses, and key findings.

Risk of Bias Assessment

Following data extraction, 2 reviewers independently assessed the risk of bias (RoB) at the outcome level using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) or adaptations of the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies as described by Wolfe et al. (2020) [18]. Disagreements were resolved by discussion or arbitration by a third reviewer.

Synthesis and Statistical Methods

Data were combined with Wolfe et al. (2020) findings by outcome to evaluate the availability of quantitative evidence, as well as the feasibility and appropriateness of meta-analysis [18].

Meta-analyses were conducted when 2 or more study reported evidence that was not clinically heterogenous as described by Wolfe et al. (2020) [18]. Briefly, random effect models were used, and statistical heterogeneity was assessed using the I^2 statistic, with a threshold of 50% or higher suggesting potentially important heterogeneity. Forest plots were used to present meta-analyses. Evidence was summarized narratively when meta-analysis was deemed inappropriate. All analyses were conducted using the Review Manager software (Version 5.4) [100].

APPENDIX B. PRISMA FLOW DIAGRAM FOR REVIEW UPDATE