BMJ Open  Safety of influenza vaccination during pregnancy: a systematic review

Dianna M Wolfe, Deshayne Fell, Chantelle Garrity, Candyce Hamel, Claire Butler, Mona Hersi, Nadera Ahmadzai, Danielle B Rice, Leila Esmailisaraji, Alan Michaud, Charlene Soobiah, Marco Ghassemi, Paul A Khan, Angela Sinilaitse, Becky Skidmore, Andrea C Tricco, David Moher, Brian Hutton

ABSTRACT

Objective We conducted a systematic review to evaluate associations between influenza vaccination during pregnancy and adverse birth outcomes and maternal non-obstetric serious adverse events (SAEs), taking into consideration confounding and temporal biases.

Methods Electronic databases (Ovid MEDLINE ALL, Embase Classic+Embase and the Cochrane Central Register of Controlled Trials) were searched to June 2021 for observational studies assessing associations between influenza vaccination during pregnancy and maternal non-obstetric SAEs and adverse birth outcomes, including preterm birth, spontaneous abortion, stillbirth, small-for-gestational-age birth and congenital anomalies. Studies of live attenuated vaccines, single- or quadrivalent vaccines, and seasonal versus pandemic vaccines, and seasonal versus no vaccination were reviewed. Control for confounding and temporal biases was inconsistent across studies, limiting pooling of data. Meta-analyses for preterm birth, spontaneous abortion and small-for-gestational-age birth demonstrated no significant associations with seasonal influenza vaccination. Immortal time bias was observed in a sensitivity analysis of meta-analysing risk-based preterm birth data. In descriptive summaries for stillbirth, congenital anomalies and maternal non-obstetric SAEs, no significant association with increased risk was found in any studies. All evidence was of very low certainty.

Conclusions Evidence of very low certainty suggests that seasonal influenza vaccination during pregnancy is not associated with adverse birth outcomes or maternal non-obstetric SAEs. Appropriate control of confounding and temporal biases in future studies would improve the evidence base.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used robust systematic review methods and restricted meta-analyses to studies that adjusted for confounding and accounted for temporal biases while focusing syntheses on outcome definitions that matched accepted criteria.

⇒ The available evidence was associated with limitations related to between-study inconsistencies in methods for adjustments for confounding and immortal time bias and variability in outcome definitions.

⇒ Outcomes assessed using the Grading of Recommendations, Assessment, Development and Evaluation framework were judged to have very low certainty of evidence.

INTRODUCTION

Maternal influenza vaccination during pregnancy can reduce influenza and associated complications among pregnant women and newborn children throughout the first months of life. The WHO has recommended vaccination of pregnant women since 2005, and many countries have adopted guidance advising vaccination of all pregnant women with a licensed, recommended, age appropriate, inactivated influenza vaccine, regardless of trimester. The safety profile of influenza vaccines during pregnancy is considered favourable; however, the evidence base is continually evolving, warranting ongoing synthesis of new data.

Most studies on this topic have used observational designs. Such studies are susceptible to bias, including confounding bias, if appropriate methods are not used to control for critical confounders (eg, maternal age, sociodemographic characteristics), as well as temporal biases, such as immortal time bias, if appropriate study design or statistical
Methods are not used. Confounding and immortal time bias can substantially impact both the magnitude and direction of results if not adequately addressed. Additionally, other complex temporal issues may further distort results, such as the seasonality of the influenza disease in many countries, the restricted availability of influenza vaccinations to specific times of the year, annual changes to the viral strains circulating and present in vaccines, and reduced opportunity for vaccination during pregnancy in women with shorter gestations (ie, preterm birth (PTB)).

Previous systematic reviews of influenza vaccination during pregnancy have generally used all-or-nothing approaches to synthesis and have elected to either (A) pool all data, often without considering study design, interventions (eg, multivalent seasonal influenza vaccines and monovalent 2009–2010 A/H1N1 influenza pandemic vaccines), confounding bias, immortal time bias or reporting format or (B) summarise all data descriptively due to concerns about heterogeneity of study designs, interventions and reporting formats reducing the validity of pooled results. Neither approach is ideal—robust strategies are needed to restrict meta-analysis to studies meeting important methodological and statistical considerations on an outcome-by-outcome basis and to address pooling of different measures of effect. We conducted a systematic review and meta-analyses to address the following review question, taking into consideration the potential impacts of confounding and temporal biases, and stratifying by seasonal and 2009 pandemic A/H1N1 influenza vaccines: Are influenza vaccines received at any time during pregnancy safe for women and their unborn children, compared with no influenza vaccination?

**METHODS**

**Protocol, registration and reporting**

A review protocol was developed a priori, guided by established systematic review methodology and registered on the Open Science Framework (OSF; doi 10.17605/OSF.IO/XEY2K) and with PROSPERO (CRD42020159030). The original protocol included a second review question regarding the efficacy/effectiveness of influenza vaccination during pregnancy against influenza outcomes; the focus of this manuscript is solely on vaccine safety. A full technical report describing our findings for both review questions is available on the OSF (https://osf.io/xey2k/). A summary of minor protocol amendments has been provided in online supplemental file 1, section 1.

This manuscript has been written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 statement.

**Patient and public involvement**

No patients or the public were involved in the performance of this systematic review.

**Study eligibility criteria**

Table 1 summarises the study eligibility criteria. We sought observational studies that assessed the safety of any seasonal or pandemic influenza vaccine not contraindicated for pregnant women, given at any time during pregnancy. Randomised controlled trials (RCTs) were excluded for this review of safety outcomes, given the rarity of most birth outcomes of interest (ie, RCTs were underpowered for these outcomes) and given the different settings of RCTs (lower-to-middle-income countries) on this topic compared with observational studies (high-income countries) that would increase clinical and statistical heterogeneity. All birth outcome data from RCTs have previously been pooled in other recent publications and are summarised in the Discussion section.

<table>
<thead>
<tr>
<th>Study designs</th>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Prospective and retrospective cohort studies</td>
<td>Seasonal and pandemic influenza vaccines of any valency administered during pregnancy that were not contraindicated during pregnancy (eg, live-attenuated vaccines)</td>
</tr>
<tr>
<td>Case–control and test-negative studies</td>
<td>Excluded: single-arm cohort studies, studies based on databases of voluntary reporting or surveillance of adverse events, abstracts</td>
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</table>

**Language**

English and French

**Table 1** Study eligibility criteria

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**Description of methods**

A brief description of the most pertinent review methods is provided in table 2, while a complete description of our methods is reported in online supplemental file 1, section 2. Briefly, we searched multiple literature databases, using a comprehensive search strategy. A liberal accelerated approach was used for title/abstract screening, while dual independent methods were used for full-text screening, data extraction and risk of bias (ROB) assessment. Pairwise meta-analyses were conducted, where two or more studies met strict inclusion criteria for meta-analysis, including accounting for confounding and/or temporal biases. ORs and risk ratios (RRs) were...
Table 2  Overview of review methods

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<tr>
<th>Review stage</th>
<th>Details</th>
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| Literature search     | As per protocol for review of both efficacy and safety outcomes, separate search strategies were developed for observational studies (MEDLINE and Embase), RCTs (Ovid MEDLINE ALL, Embase Classic+Embase and the Cochrane Central Register of Controlled Trials), and systematic reviews (Ovid platform: Ovid MEDLINE ALL, Embase Classic+Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment). Study design filters were applied for RCTs and systematic reviews. No language or date restrictions were used. Search strategies are provided in online supplemental file 1, section 3. Searches were peer reviewed using Peer Review of Electronic Search Strategies (PRESS) Checklist. Searches were run 11 December 2019 and updated to 3 June 2021. Bibliographies of included systematic reviews and primary studies were screened. Grey literature searching (June 2020) included clinical trial registries and other platforms, and was guided by the Canadian Agency of Drugs and Technologies in Health (CADTH) Grey Matters Checklist.  
Study selection         | Search results were deduplicated in Reference Manager* (original search) or EndNote† (update) prior to being uploaded to online review management software DistillerSR. Two levels of screening were performed (title/abstract and full text), with pilots at each level. A liberal accelerated approach was used to screen titles/abstracts (one reviewer to include, two to exclude), while dual independent screening was used for full texts. Conflict resolution was through discussion.  
Data extraction         | Dual independent data extraction was performed in DistillerSR, using standardised piloted forms. Conflict resolution was reached through discussion. Data extraction files have been made available online (see online supplemental files 2–4).  
Study characteristics collected: author, year of publication, language, design, objective, funding, whether conflicts of interest were declared, country of conduct, study period and influenza seasons, longest follow-up, sample size, inclusion criteria, method of measurement of gestational age.  
Demographic data collected: maternal age, race, gestational age at vaccination, maternal comorbidities, whether specific maternal risk factors were reported, proportion vaccinated.  
Intervention data collected: vaccine type (seasonal or pandemic), valency, name, presence of adjuvant, strains, setting of vaccine delivery.  
Outcome data (all outcome definitions and time points were extracted): numbers of events and participants per group, and, if reported, point estimate with 95% CI, whether confounding was controlled and the confounders that were controlled, including three critical confounders: maternal age, smoking during pregnancy, and socioeconomic status.  
Country income level was determined for each study as per The World Bank World Development Indicators.  
Risk of bias            | Dual independent assessment using adaptations of the Newcastle-Ottawa Scale (NOS) for cohort and case–control studies, with conflict resolution through discussion. NOS scores can range from 0 to 9, with lower scores representing higher ROB. Suggested score cut-offs are as follows: low ROB (7–9), some concerns (4–6), high ROB (0–3). Details regarding the different ROB domains are provided in online supplemental file 1, section 4.  
Data synthesis/Statistical methods | Data were cleaned and collated in Microsoft Excel, and tables summarising study characteristics were developed separately for cohort and case–control studies. Results data were tabulated to assess feasibility of meta-analyses. ORs and risk ratios (RRs) were considered equivalent, given the rarity of the outcomes of interest and anticipated small effects of vaccination. HRs were considered approximate to RRs, ORs and incidence RRs, given short follow-up periods (eg, duration of gestation), rarity of events and small effects. Pairwise meta-analyses using random effects models were considered when two or more studies reported findings that were adjusted for confounding (and immortal time bias, where appropriate; see online supplemental file 1, section 2 for a brief discussion of immortal time bias) for a given outcome definition, time point and comparison, and when the available evidence was not clinically heterogeneous. Approaches to handle confounding that were of interest included matching, multivariable adjustment and propensity score methods. Where study effect estimates for meta-analysis were heterogeneous (eg, both RRs and ORs), meta-analyses were conducted and reported using RRs. Effect estimates <1 indicated reduced risk of event for vaccinated subjects (ie, greater safety). Statistical heterogeneity was assessed with the I² statistic, where values ≥50% suggested important heterogeneity. Statistical heterogeneity was explored using stratified analyses, and studies were pooled if no important differences in study characteristics were found. All meta-analyses were conducted in Comprehensive Meta-analysis Software (V3.3.070, Biostat, Englewood, New Jersey, USA). Descriptive summaries were developed for prioritised definitions, when meta-analysis was not feasible, guided by the Synthesis without Meta-analysis statement.  
Continued
considered to approximate each other, given the rarity of events and small anticipated effects of vaccination. Assessment of the certainty of evidence followed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. Outcomes reported in the main manuscript were prioritised according to GRADE methods as detailed in table 2, and syntheses for these outcomes have been reported in the main text along with secondary syntheses that provide context to the prioritised findings.

RESULTS

Availability of the literature

Of 9443 unique references identified by our searches, 504 full texts were assessed and 93 were included in the original review. Eight RCTs reported in 16 references, 126–40 full texts were assessed and 93 were included in the original review. Eight RCTs reported in 16 references, 126–40

Table 2

<table>
<thead>
<tr>
<th>Review stage</th>
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<tbody>
<tr>
<td>Assessment of level of evidence</td>
<td>Strength and certainty of evidence were assessed following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework, using GRADEpro GDT online software (<a href="https://gradepro.org/">https://gradepro.org/</a>). Syntheses were prioritised for assessment based on outcome definition (as per the GAIA Network and Brighton Collaboration Network); see online supplemental file 1, section 2, intervention/comparison (trivalent inactivated influenza vaccine or quadrivalent inactivated influenza vaccine vs no vaccine), content expert prioritisation exercise, and analysis type (full-sample analyses only). Dual independent assessment was conducted, with discussion of conflicts.</td>
</tr>
<tr>
<td>Reporting</td>
<td>Only findings from GRADE-prioritised syntheses and secondary syntheses that provide additional context have been reported in the main text; all other seasonal influenza vaccine results are reported in online supplemental file 1, section 5 or as raw data in online supplemental files 2–4. RoB has been summarised across studies, using each study’s primary outcome with the lowest RoB. Study-level RoB data have been provided in online supplemental file 1, section 6. GRADE lay statements and Summary of Findings tables have been reported in the main text, with an Evidence Profile table provided in online supplemental file 1, section 7. Syntheses and/or data for vaccines other than seasonal influenza (eg, pandemic vaccines, combinations of seasonal and pandemic vaccines) have been provided in online supplemental file 1, sections 8–11 and online supplemental files 2–4.</td>
</tr>
</tbody>
</table>

*Reference Manager, V.12.0.3, Thomson Reuters.
†EndNote, V.X9.3.3, Clarivate.
§RoB, risk of bias.
and 1 case–control study evaluating stillbirths that did not adjust for SES. Additional details can be found in online supplemental files 2–4.

**ROB assessment**

Across all studies, the most prevalent ROB concerns were related to lack of appropriate adjustment for confounding (‘comparability bias’ in 62% of studies; figure 2). Twenty-one studies (72%) were judged to have an overall low ROB, while eight were judged to have a moderate ROB. A domain-level summary of ROB by study and the original outcome-level ROB data files have been provided in online supplemental file 1, section 6 and online supplemental files 2–4.

**Syntheses of prioritised outcomes**

Table 4 summarises all synthesis findings for the prioritised outcomes. Numbers of mothers or infants included in individual study analyses and overall in each meta-analysis are provided in the associated forest plots (see figures 3 and 4).

**Preterm birth**

Fifteen cohort studies assessed TIIV at any time during pregnancy on the occurrence of PTB (<37 completed gestational weeks; table 4). Five studies accounted for immortal time bias and confounding and were included in the prioritised meta-analysis, while nine studies were pooled in a secondary synthesis to evaluate differences in pooled results when temporal biases were not considered. A final study was descriptively summarised in online supplemental file 1, section 5 due to insufficient details about its analytic methods.

**Prioritised synthesis**

The estimated adjusted HR (aHR) of PTB for women who received TIIV during pregnancy was 1.08 (95% CI 0.89 to 1.30, I²=28.2; 5 studies, >152,476 women; figure 3). The evidence was assessed to be of very low certainty due to concerns regarding to ROB and inconsistency (table 4). One large high-quality study reported an association close to the null value of 1 was weighted heavily (55.6%; n=145,867). There was a trend of decreasing effect size over time, based on date of publication.

**Secondary syntheses**

In the meta-analysis of nine studies (n>151,032) that did not consider temporal biases, the estimated adjusted RR (aRR) of PTB for women who received TIIV during pregnancy was 0.86 (95% CI 0.76 to 0.97, I²=71.1; figure 4, Any trimester, lower plot). Additionally, statistical heterogeneity was high, potentially due to differences in the...
## Table 3 Characteristics of the 24 cohort studies and 5 case–control studies that compared seasonal influenza vaccination (TIIV and or QIIV) to no vaccination

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of conduct; design; funding</th>
<th>Recruitment period</th>
<th>No of women (infants)</th>
<th>Interventions (cohort studies)/exposure window (case–control studies)</th>
<th>Safety endpoints</th>
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<tbody>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
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</tr>
<tr>
<td>McMorrow et al, 2020</td>
<td>South Africa; RC; Non-industry</td>
<td>Women who sought antenatal care between 14 May 2015–16 August 2015 and 1 April 2016–25 August 2016</td>
<td>4084 (4084)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>Stillbirths, PTB, LBW, SGA</td>
</tr>
<tr>
<td>Mohammed et al, 2020</td>
<td>Australia; PC; No funding</td>
<td>First antenatal appointment between March 2015 and December 2017</td>
<td>1253 (1201)</td>
<td>Seasonal vaccine (TIIV)</td>
<td>PTB, LBW, SGA, SAB, CA</td>
</tr>
<tr>
<td>Ohfuji et al, 2020</td>
<td>Japan; PC; Non-industry</td>
<td>Attended antenatal clinic between October and December 2013, prior to the 2013/2014 influenza season</td>
<td>10330 (NR)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>SAB, stillbirths, PTB, LBW, CA</td>
</tr>
<tr>
<td>Speake et al, 2020</td>
<td>Australia; RC; Non-industry</td>
<td>Date of conception estimated to have occurred between December and July, from April 2012 to July 2015</td>
<td>70838 (70 838)</td>
<td>Seasonal vaccine (TIIV and QIIV) No vaccine</td>
<td>Stillbirths, PTB, SGA</td>
</tr>
<tr>
<td>McHugh et al, 2019</td>
<td>Australia; RC; Non-industry</td>
<td>Pregnant between 1 December 2003 and 31 December 2006 or between 1 January 2009 and 31 June 2011</td>
<td>576 (697)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, SGA</td>
</tr>
<tr>
<td>McHugh et al, 2019</td>
<td>Australia; PC, post hoc analysis; Non-industry</td>
<td>Within 55 days of birth from 1 April 2012 to 31 December 2015; recruitment maximised during influenza seasons (April–October)</td>
<td>8827 (8,827)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, SGA</td>
</tr>
<tr>
<td>Singh et al, 2019</td>
<td>India; RC; NR</td>
<td>Pregnant and vaccinated or refused vaccination between January 2016 and March 2018</td>
<td>346 (348)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>Maternal SAEs, PTB</td>
</tr>
<tr>
<td>Ohfuji et al, 2018</td>
<td>Japan; PC; Non-industry</td>
<td>Pregnant between September and December 2013</td>
<td>3044 (3044)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, CA</td>
</tr>
<tr>
<td>Arriola et al, 2017</td>
<td>Nicaragua; PC/RC; Non-industry</td>
<td>Births from 21 July 2014 to 4 December 2014</td>
<td>3268 (3268)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, SGA</td>
</tr>
<tr>
<td>McHugh et al, 2017</td>
<td>Australia; Nested RC; Non-industry</td>
<td>Births from 1 April 2012 to 31 December 2014</td>
<td>7126 (7126)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW</td>
</tr>
<tr>
<td>Zerbo et al, 2017</td>
<td>USA; RC; Non-industry</td>
<td>Births from 1 January 2010 to 31 December 2015</td>
<td>145869 (145 869)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, SGA</td>
</tr>
<tr>
<td>Chambers et al, 2016</td>
<td>USA and Canada; PC; Mixed</td>
<td>Pregnant between 2010 and the end of 2014</td>
<td>1730 (1707)</td>
<td>Seasonal vaccine (TIIV and QIIV) No vaccine</td>
<td>SAB, stillbirths, PTB, SGA</td>
</tr>
<tr>
<td>Olsen et al, 2016</td>
<td>Laos; PC; Non-industry</td>
<td>Births from April 2014 to February 2015</td>
<td>5103 (5103)</td>
<td>Seasonal vaccine (TIIV by Afluria) No vaccine</td>
<td>PTB, SGA</td>
</tr>
<tr>
<td>Regan et al, 2016</td>
<td>Australia; RC; Non-industry</td>
<td>Births from 1 April 2012 to 31 December 2013</td>
<td>58008 (57 660)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>Stillbirths</td>
</tr>
<tr>
<td>Ahrens et al, 2014</td>
<td>USA; RC (control group from a case–control study); Non-industry</td>
<td>Pregnant and vaccinated or matched by LMP to vaccinated group from 2006 to 2010</td>
<td>1619 (1619)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, SGA</td>
</tr>
<tr>
<td>Legge et al, 2014</td>
<td>Canada; RC; No funding</td>
<td>Births from 1 November 2010 to 31 March 2012</td>
<td>12223 (11 293)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, SGA</td>
</tr>
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<tr>
<th>Study</th>
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<tr>
<td>Nordin et al., 2014^65</td>
<td>USA; RC; Non-industry and Insurance</td>
<td>Pregnant during influenza seasons between 2004/2005 and 2008/2009</td>
<td>150089 (150 089)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, SGA</td>
</tr>
<tr>
<td>Adedinsendo et al., 2013^66</td>
<td>USA; RC; Non-industry and Insurance</td>
<td>Births from 1 January 2005 to 31 December 2008</td>
<td>5422 (NR)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, SGA</td>
</tr>
<tr>
<td>Nordin et al., 2013^59</td>
<td>USA; RC; Non-industry and Insurance</td>
<td>Pregnant between 1 June 2002 and 31 July 2009 and vaccinated or matched</td>
<td>223898 (NA)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>Maternal SAEs</td>
</tr>
<tr>
<td>Dodds et al., 2012^58</td>
<td>Canada; RC; Non-industry</td>
<td>Births from 1 April 2006 to 31 October 2009</td>
<td>9647 (9647)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, LBW, SGA</td>
</tr>
<tr>
<td>Sheffield et al., 2012^100</td>
<td>USA; PC; NR</td>
<td>Pregnant between October and March in 2003–2008</td>
<td>84843 (85 783)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>CA, stillbirths, PTB, LBW</td>
</tr>
<tr>
<td>Omer et al., 2011^94</td>
<td>USA; RC; Non-industry</td>
<td>Births from 1 June 2004 to 30 September 2006</td>
<td>4168 (NR)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB, SGA</td>
</tr>
<tr>
<td>Munoz et al., 2005^68</td>
<td>USA; RC; Non-industry</td>
<td>Pregnant during influenza seasons from 1 July 1998 to 30 June 2003</td>
<td>1051 (1051)</td>
<td>Seasonal vaccine (TIIV by Aventis Pasteur or Wyeth) No vaccine</td>
<td>Maternal SAEs, PTB, CA</td>
</tr>
<tr>
<td>Black et al., 2004^61</td>
<td>USA; RC; NR</td>
<td>Births between November and February from November 1997 to February 2002</td>
<td>49585 (48 639)</td>
<td>Seasonal vaccine (TIIV) No vaccine</td>
<td>PTB</td>
</tr>
<tr>
<td>Case–control studies</td>
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<tr>
<td>Panagiotakopoulou et al., 2020^179</td>
<td>USA; RCC; Non-industry</td>
<td>Pregnancies ending in live or stillbirth from 1 January 2012 to 30 September 2015</td>
<td>3975</td>
<td>Seasonal vaccine (TIIV, with or without Tdap), 14 days after last menstrual period through 7 days before index date</td>
<td>Stillbirths</td>
</tr>
<tr>
<td>Donahue et al., 2019^111</td>
<td>USA; RCC; Non-industry</td>
<td>Pregnant during the 2012–2013, 2013–2014 or 2014–2015 influenza seasons</td>
<td>2472</td>
<td>Seasonal vaccine (TIIV) 1–28 days after conception, &gt;28 days after conception and 1–28 days before SAB</td>
<td>SAB</td>
</tr>
<tr>
<td>Donahue et al., 2017^110</td>
<td>USA; RCC; Non-industry</td>
<td>During the 2010–2011 or 2011–2012 influenza seasons</td>
<td>970</td>
<td>Seasonal vaccine (TIIV) 1–28 days after SAB</td>
<td>SAB</td>
</tr>
<tr>
<td>Louik et al., 2016^185</td>
<td>USA; RCC; Mixed</td>
<td>During the 2011–2012, 2012–2013 or 2013–2014 influenza vaccine seasons</td>
<td>1910</td>
<td>Seasonal vaccine (TIIV or QIIV) during first trimester</td>
<td>CA</td>
</tr>
<tr>
<td>Irving et al., 2013^113</td>
<td>USA; RCC; Non-industry</td>
<td>During the 2005–2006 or 2006–2007 influenza seasons</td>
<td>486</td>
<td>Seasonal vaccine (TIIV) any time during pregnancy and 1–28 days before SAB</td>
<td>SAB</td>
</tr>
</tbody>
</table>

CA, congenital anomalies; LBW, low birth weight; NR, not reported; PC, prospective cohort; PTB, preterm birth; QIIV, quadrivalent inactivated influenza vaccine; RC, retrospective cohort; RCC, retrospective case–control; SAB, spontaneous abortion; SAE, serious adverse events; SGA, small-for-gestational-age birth; Tdap, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis; TIIV, trivalent inactivated influenza vaccine.
background risk of PTB (range: 6%–16%) in different study populations and variation in the outcome definitions (eg, lower limits of gestational age at birth).

Six studies (n>47,211) reported adjusted findings for first trimester vaccination and were included in a meta-analysis. The lower gestational age limit of the PTB definitions ranged from >20 weeks to ≥28 weeks. All studies were at a reduced risk of temporal bias because first-trimester vaccination, by definition, occurred before the at-risk period for PTB. Four studies further reduced temporal bias through statistical methods and two did not. The estimated aHR of PTB for women who received TIIV during their first trimester was 1.05 (95% CI 0.92 to 1.20, I²=30.5; figure 4, First trimester).

Spontaneous abortion
Five studies evaluated the effect of TIIV during pregnancy on the occurrence of spontaneous abortion (SAB) under 20 gestational weeks. However, because one study did not adjust for confounding and different exposure windows were assessed, only two studies were pooled.

Prioritised synthesis
Both studies (n=1900) assessed an exposure window of up to 20 gestational weeks and accounted for immortal time bias. The estimated aHR of SAB for women who received TIIV during pregnancy was 0.77 (95% CI 0.31 to 1.89; I²=37.5; figure 4). This evidence was of very low certainty due to serious concerns regarding ROB, inconsistency and imprecision (table 4). Neither study restricted events to the influenza season, therefore, some of the included women may not have had the opportunity for exposure to either influenza vaccine or virus.

Secondary syntheses
Two case–control studies conducted by the same investigators used an exposure window of 1–28 days before the index date (ie, date of SAB for cases or the equivalent time postconception for controls). The initial study (n=782) was conducted during the first two influenza seasons following the 2009 A/H1N1 pandemic and found a significant association between SAB and TIIV received within 1–28 days before the index date during the first postpandemic season (2010–11 adjusted OR (aOR) 3.70, 95% CI 1.40 to 9.40), but not during the second season (2011–2012 aOR=1.40, 95% CI 0.60 to 3.30). When women were stratified by receipt of monovalent A/H1N1 2009 pandemic vaccine in the previous year, the association remained significant only for those who had received pandemic vaccine. A second case–control study (n=1934) spanning the three influenza seasons between 2012 and 2015 was conducted to evaluate the interaction between previous year vaccination and TIIV or QIV exposure during pregnancy. No interaction was found and, overall, the estimated aOR of SAB for women who received TIIV or QIV during pregnancy was 0.80 (95% CI 0.60 to 1.10). Very high statistical heterogeneity (I²=86.0%) precluded meta-analysis of the two studies.

Stillbirth
Seven studies reported data for stillbirth occurring ≥18–22 gestational weeks or with birth weight ≥500 g. Two studies that evaluated vaccination at any time during pregnancy and reported results of adjusted analyses that accounted for immortal time bias were pooled; however, very high statistical heterogeneity was found (I²=82.9), potentially due to differences in study designs, covariates considered to be confounders, and methods used to control confounding. The high heterogeneity suggested that pooling was inappropriate due to differences between the two studies; thus, the pooled results have not been reported and the studies have been descriptively summarised.

Prioritised synthesis
In a cohort study, the estimated aHR of stillbirth for women who received TIIV during pregnancy was 0.49 (95% CI 0.29 to 0.83; n=50,008), while in a case–control study, the estimated aOR of stillbirth for TIIV or QIV received between 14 days after the last menstrual period.
Table 4  Summary of findings table of GRADE-prioritised outcomes synthesised from 29 included observational studies that compared seasonal influenza vaccination (TIIV and or QIIV) to no vaccination

<table>
<thead>
<tr>
<th>Outcome no of participants (studies)</th>
<th>Relative effect (95% CI)</th>
<th>Without seasonal influenza vaccine</th>
<th>With seasonal influenza vaccine</th>
<th>Difference</th>
<th>Certainty</th>
<th>GRADE lay statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth (&lt;37 completed weeks)</td>
<td>HR 1.08 (0.89 to 1.30)</td>
<td>Low baseline risk</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3.2% (2.9 to 4.2)</td>
<td>3.5%</td>
<td>0.3% more (0.3 fewer to 1 more)</td>
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<tr>
<td></td>
<td>High baseline risk</td>
<td>15.0% (13.5 to 19.4)</td>
<td>16.2%</td>
<td>1.2% more (1.5 fewer to 4.4 more)</td>
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<tr>
<td>Spontaneous abortion (&lt;20 gestational weeks)</td>
<td>HR 0.77 (0.31 to 1.89)</td>
<td>Moderate baseline risk</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5.0% (1.6 to 9.2)</td>
<td>3.9%</td>
<td>1.1% fewer (3.4 fewer to 4.2 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirths (≥18–22 gestational weeks or ≥500 g)</td>
<td>Regan et al, 2016,97 reported an adjusted HR=0.49 (0.29 to 0.84) in 58008 pregnancies (5076 exposed and 52932 unexposed) in a cohort study evaluating influenza vaccination at any trimester of pregnancy. In a case–control study evaluating influenza vaccination at any trimester, Panagiotakopoulos et al,116 2020 found an aOR=0.98 (0.82 to 1.18) among 1475 cases and 12119 controls. These two studies could not be pooled due to extremely high heterogeneity (I²=82.85).</td>
<td>RR 0.99 (0.95 to 1.04)</td>
<td>Low baseline risk</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3.7% (3.5 to 3.8)</td>
<td>3.7%</td>
<td>0.0% fewer (0.2 fewer to 0.1 more)</td>
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<tr>
<td></td>
<td>Moderate baseline risk</td>
<td>6.0% (5.7 to 6.2)</td>
<td>5.9%</td>
<td>0.1% fewer (0.3 fewer to 0.2 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High baseline risk</td>
<td>13.6% (12.9 to 14.1)</td>
<td>13.5%</td>
<td>0.1% fewer (0.7 fewer to 0.5 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-for-gestational-age birth (&lt;10th percentile)</td>
<td>No of participants: 297424 (11 observational studies)</td>
<td>RR 0.99 (0.95 to 1.04)</td>
<td>Low baseline risk</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3.7% (3.5 to 3.8)</td>
<td>3.7%</td>
<td>0.0% fewer (0.2 fewer to 0.1 more)</td>
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<tr>
<td></td>
<td>Moderate baseline risk</td>
<td>6.0% (5.7 to 6.2)</td>
<td>5.9%</td>
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</tr>
<tr>
<td>Congenital anomalies from birth to 6 months of age</td>
<td>No of participants: 4277 (one observational study)</td>
<td>RR 0.99 (0.95 to 1.04)</td>
<td>Low baseline risk</td>
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<tr>
<td></td>
<td>3.7% (3.5 to 3.8)</td>
<td>3.7%</td>
<td>0.0% fewer (0.2 fewer to 0.1 more)</td>
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<tr>
<td>Congenital anomalies from birth to discharge</td>
<td>No of participants: 1207 (1 observational study)</td>
<td>RR 0.99 (0.95 to 1.04)</td>
<td>Low baseline risk</td>
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<tr>
<td></td>
<td>3.7% (3.5 to 3.8)</td>
<td>3.7%</td>
<td>0.0% fewer (0.2 fewer to 0.1 more)</td>
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</table>

Continued
<table>
<thead>
<tr>
<th>Outcome no of participants (studies)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Certainty</th>
<th>GRADE lay statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal serious non-obstetrical adverse events; events unrelated to pregnancy causing hospitalisation</td>
<td>Single study Munoz et al,(^8) 2005 found no apparent difference in risk between TIIV vaccinated (2 in 225) and unvaccinated women (3 in 826).</td>
<td>Without seasonal influenza vaccine</td>
<td>With seasonal influenza vaccine</td>
<td>Difference</td>
</tr>
<tr>
<td>No of participants: 1051 (1 observational study)</td>
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</tr>
<tr>
<td></td>
<td>Maternal serious non-obstetrical adverse events: events unrelated to pregnancy causing hospitalisation</td>
<td>No events found in a single study Singh et al,(^103) 2019 of 288 TIIV vaccinated and 58 unvaccinated women.</td>
<td>Without seasonal influenza vaccine</td>
<td>With seasonal influenza vaccine</td>
</tr>
<tr>
<td>No of participants: 346 (one observational study)</td>
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</tr>
<tr>
<td>Maternal serious non-obstetrical adverse events: inpatient Guillain–Barré syndrome</td>
<td>Single study Nordin et al,(^95) 2013 found no significant difference between TIIV vaccinated (0 in 75 906) and unvaccinated women (1 in 147 992) (p=0.34).</td>
<td>Without seasonal influenza vaccine</td>
<td>With seasonal influenza vaccine</td>
<td>Difference</td>
</tr>
<tr>
<td>No of participants: 223 898 (1 observational study)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: we are uncertain in the effect estimate: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

* Four of five studies scored ≥7 and the fourth scored 6; however, there were concerns regarding the representativeness of the exposed cohort (selection bias) in four studies, the adequacy of follow-up in two studies, and assessment of the confidence intervals in one study and assessment of the outcome in two studies.
† The 95% CIs of the most heavily weighted study does not encompass the effect estimates of the three moderately weighted studies.
‡ The total sample size met the criteria for optimal information size, but the total number of events did not.
§ There were concerns regarding selection bias in both of the included studies.
¶ Initial postpandemic study found significantly increased risk, whereas no other study found significant effects.
** Neither of the CIs of the two studies contains the other’s effect estimate.
†† The p value of the Q estimate for the meta-analysis was >0.05 and two heavily weighted studies were consistent; however, most of the minimally weighted studies had point estimates that did not fall within all other confidence intervals.
‡‡ Serious ROB due to inadequate case definition, the unclear representativeness of the cases and unclear non-response rate.
§§ Concerns regarding bias related to selection and outcome assessment.
¶¶ Total sample size is much lower than the optimal information size for the control group risk.
*** "Potential serious bias due to lack of reporting of follow-up time and follow-up methods in unvaccinated group, leading to potential bias for the following domains: ‘Could outcome be present at the start of study for unvaccinated women?’, ‘Was follow-up time long enough for outcome to occur?’ and ‘Were unvaccinated women followed adequately?’.
††† Although country/countries of conduct was/were low income to middle income, the outcome shouldn’t be substantially different in the Canadian context.
\(\text{aOR, adjusted OR; ARR, adjusted risk ratio; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; QIV, trivalent inactivated influenza vaccine; SAE, serious adverse event; TIIV, trivalent inactivated influenza vaccine.}\)
Figure 3  Forest plots of studies reporting adjusted analyses for preterm birth, by timing of vaccine administration.*Denotes outcomes for which meta-analysis could not be conducted. Forest plots for these outcomes illustrate effects reported in studies that were descriptively summarized. Risk of bias was assessed using the 9-point Newcastle-Ottawa Scale. Higher values are associated with lower risk of bias. Numbers followed by plus signs (+) are lower than the actual total numbers included in the meta-analysis due to unreported raw data in one or more studies. aOR, adjusted odds ratio; aRR, adjusted risk ratio; NR, not reported; ROB, risk of bias; TIIV, trivalent inactivated influenza vaccine.
and 7 days before the index date was 0.98 (95% CI 0.81 to 1.17; n=3975; did not adjust for SES; figure 4). A very low certainty of evidence was assessed due to concerns regarding inconsistency between the two studies (table 4).

Secondary syntheses

The aforementioned cohort study97 also reported stratified analyses for gestational age at birth (preterm and full term) and for timing of events with respect to the influenza season (before, during, after). Sample sizes were not reported. This study was conducted year-round in Australia and spanned two influenza seasons of differing durations. Among PTB, the estimated aHR of stillbirth for women who received TIIV during pregnancy was 0.45 (95% CI 0.26 to 0.81), but among term births, the estimated aHR of stillbirth was 1.13 (95% CI 0.27 to 4.71; figure 4). As well, in the 2.5–3 months after the influenza season, the estimated aHR of stillbirth for women who received TIIV during pregnancy was 0.33 (95% CI 0.12 to 0.88), but the effect was not significant in the 3–4 months during (aHR 0.57, 95% CI 0.25 to 1.31) or the 2–6.5 months before the influenza season (aHR 0.60, 95% CI 0.22 to 1.61; figure 4).

Another cohort study104 that accounted for immortal time bias through design and assessed only first trimester vaccination found the estimated aRR of stillbirth to be 1.18 (95% CI 0.64 to 2.18; n=11955).

Small-for-gestational-age birth

Thirteen studies evaluated the association between TIIV received during any trimester and SGA birth.53 57 58 64 68 77 85–87 90 93 94 108 One reported findings from unadjusted analyses85 and 1 did not report statistical methods sufficiently,86 leaving 11 studies for meta-analysis.55 57 58 64 68 77 87 90 93 94 108

Prioritised synthesis

Two90 108 of 11 studies included in the meta-analysis comprised almost 75% of the pooled estimate by weight and reported aRRs of 1.00; the estimated pooled aRR of SGA for women who received TIIV during any trimester was 0.99 (95% CI 0.95 to 1.04, I2=15.8; n>297424; figure 4). Three studies did not adjust for smoking during pregnancy.58 90 93 A very low certainty of evidence was assessed due to concerns regarding inconsistency (table 4).

Congenital anomalies

Four studies87 91 102 115 evaluated the association between TIIV or QIIV during the first trimester and the occurrence of congenital anomalies identified either at birth87 91 102 or up to 6 months of age.115 Two studies (one cohort87 and one case–control115) adjusted for confounding but used differing periods to ascertain anomalies in infants (ie, at birth and up to 6 months of age), precluding meta-analysis.

Figure 4  Forest plots of studies reporting adjusted analyses for the prioritised adverse birth outcomes. ITB, immortal time bias; NR, not reported; ROB, risk of bias; TIIV, trivalent inactivated influenza vaccine. Numbers followed by plus signs (+) are lower than the actual total numbers included in the meta-analysis due to unreported raw data in one or more studies.
Prioritised synthesis

TIIV or QIIV during the first trimester was not significantly associated with congenital anomalies in either of the studies, whether ascertainment occurred at birth (aOR: 0.33, 95% CI 0.04 to 2.73; n=1207) or up to 6 months of age (aOR: 1.01, 95% CI 0.85 to 1.21; n=4277; figure 4). Both studies included both live and stillborn infants from multiple seasons.87 115 The certainty of the evidence was assessed to be very low due to ROB at both time points (table 4).

Maternal non-obstetric serious adverse events

Three cohort studies reported non-obstetric serious adverse events (SAEs).88 89 103 One study89 adjusted for confounders and found no significant association with Guillain-Barre syndrome within 42 days postvaccination (p=0.34; vaccinated: 0 events/75906 women, unvaccinated: 1 event/147992 women). The other two studies reported raw data only: no significant associations with non-obstetric hospitalisations within 42 days postvaccination88 (vaccinated: 2 events/225 women, unvaccinated: 3 events/826 women; RR: 2.45, 95% CI 0.41 to 14.56) or with SAEs over an unknown follow-up period103 (vaccinated: 0 events/288 women, unvaccinated: 0 events/58 women). Events were rare for all outcomes and sample sizes potentially too small to detect significant differences between groups. All maternal SAE outcomes were assessed with a very low certainty of evidence due to concerns regarding imprecision (table 4).

DISCUSSION

Our systematic review of the safety of seasonal influenza vaccination during pregnancy was designed to ensure our findings were relevant to currently used multivalent products that may have a potentially different safety profile than monovalent influenza vaccines and to ensure reporting of least biased estimates. We identified no significant harmful or beneficial effects of TIIV or QIIV on birth outcomes or maternal non-obstetric SAEs among 29 studies. However, clinical, methodological and statistical heterogeneity and lack of adjustment for confounding and/or immortal time bias precluded meta-analysis for stillbirth, congenital anomalies and maternal SAEs, and reduced the number of studies available in meta-analyses of PTB, SAB and SGA. Meta-analyses for PTB and SGA were driven by one or two heavily weighted studies each. Syntheses of the effects of 2009 A/H1N1 pandemic vaccination on adverse birth outcomes demonstrated similar results (see online supplemental file 1, section 8).

Research regarding the safety of seasonal influenza vaccination during pregnancy is ongoing, with five new studies published in 2020 alone,86 87 91 104 116 warranting continued review of the literature. Recent systematic reviews have opted to either pool all available studies, regardless of vaccine type (ie, seasonal and 2009 A/H1N1 pandemic) or the presence of confounding,15 16 or not to pool any studies due to differences in vaccine types and effect estimates and the presence of confounding bias.19 To the best of our knowledge, no previous review has attempted to reduce temporal and confounding biases. Pharmacoepidemiological studies can be biased by immortal time117 if each participant’s times of enrolment, treatment start, and event occurrence are not measured, and the duration of unexposed and exposed time not accounted for through either analytical methods10 110 or study design10 111 Observational studies of vaccination during pregnancy that report time-dependent birth outcomes (eg, PTB and stillbirth10 111) are susceptible to immortal time bias if the time at risk prior to vaccination is misclassified as being exposed. Approaches, such as use of Cox proportional hazards models with a time-varying exposure variable for vaccination status correctly account for each woman’s exposed and unexposed time, reducing immortal time bias.10 113 118 Our meta-analyses for PTB demonstrated that immortal time bias can have a substantial impact on study results. When immortal time bias was not accounted for, a significant protective effect of seasonal influenza vaccination during pregnancy on PTB was observed. However, when appropriate analytical methods were used, seasonal influenza vaccination was not associated with PTB. Similar impacts of temporal biases were found in meta-analyses of the effects of 2009 A/H1N1 pandemic vaccine during pregnancy on stillbirth (see online supplemental file 1, section 8). These differences may have important implications for decision-makers and knowledge users.

Four RCTs have been conducted in pregnant women, with objectives to evaluate seasonal influenza vaccine efficacy to prevent infant lab-confirmed influenza36 38 40 and maternal influenza-like illness36 as primary outcomes. Data on adverse birth outcomes were also collected as secondary outcomes; however, due to the inherent rarity of these events, the individual studies were underpowered to detect differences between groups for these outcomes.25 Omer et al23 pooled individual patient data from three of these RCTs36 38 40 (one excluded due to small sample size46) and found that within the combined dataset of 10000 women no significant associations with adverse birth outcomes were found.23 They concluded that the pooled dataset was still substantially underpowered to detect a meaningful difference between groups for the stillbirth outcome, and moderately underpowered for all other adverse birth outcomes.25 Regan and Munoz24 pooled fetal death data from the same three RCTs36 38 and included data from the fourth RCT47 in meta-analyses of PTB, LBW and SGA birth. No increased risks of any adverse birth outcomes were found. We reported two meta-analyses that were in common with the above publications,23 24 and our findings were similar: no significant associations with PTB (aHRcurrent=1.09 (95% CI 0.89 to 1.33) vs RRcurrent=0.97 (95% CI 0.87 to 1.08) vs RRRegan=0.95 (95% CI 0.85 to 1.06)) or SGA (aRRcurrent=0.99 (95% CI 0.95 to 1.04) vs RRcurrent=0.99 (95% CI 0.93 to 1.06) vs RRRegan=0.96 (95% CI 0.90 to 1.02)). Furthermore, Regan and Munoz descriptively summarised maternal...
adverse events postinfluenza-vaccination reported in RCTs, prospective cohort studies, and postmarketing surveillance studies and found no evidence of increased safety signals beyond those found in the general public or compared with pertussis vaccine. Vaccination for seasonal influenza during pregnancy is recommended by the WHO, therefore, ethical approval of a future large-scale (≥10,000 women) RCT powered for birth outcomes is unlikely. It is encouraging that data pooled from methodologically sound observational studies can approximate findings from pooled individual patient data.

Our review has several strengths, including a broad search and use of robust systematic review methods. To reduce clinical heterogeneity and to align with currently available vaccines, we did not pool seasonal and monovalent 2009 A/H1N1 pandemic influenza vaccines. Entry into meta-analyses was restricted to least-biased estimates that were adjusted for confounding and accounted for temporal biases, where appropriate. As well, we prioritised synthesis of very focused outcome definitions that matched published accepted criteria. As a limitation, we made assumptions regarding equivalence of effect estimates (ie, RR=OR=hour); however, only the meta-analysis for SGA included heterogeneous effect estimates, and for this outcome, the assumptions behind the approximation of effect estimates were met. The available evidence was limited by inconsistent adjustment for confounding and immortal time bias and by high variability of outcome definitions and time points, which precluded pooling of some of the identified data. As well, poor reporting of detailed characteristics of the seasonal influenza vaccines in use in the study location during the study periods prevented the development of inferences regarding the effects of vaccine adjuvant or production technology (eg, egg based, cell based, recombinant). Finally, there were limitations in the use of GRADE in that only observational designs were considered for inclusion. GRADE assessment of syntheses of observational studies begins with a rating of low certainty, and evidence is only rated upward to moderate certainty if a large statistically significant effect is found. When the review objective is to assess safety (ie, no significant difference between exposure groups), large significant effects are not expected and, thus, evidence would be considered at low certainty, at best, even when well-conducted studies are included.

In conclusion, our review suggests that vaccination against seasonal influenza during pregnancy is not associated with significant safety issues, with respect to adverse birth outcomes and maternal non-obstetric SAEs. A small but non-significant association with an increased risk of PTB was found in a meta-analysis of studies that accounted for immortal time bias. This was in contrast to a significant decrease in the risk of PTB, when studies that did not account for immortal time bias were pooled. Improvements in study design and analytical methods in future studies would advance the evidence base. Additionally, although no safety signals have been identified through routine pharmacovigilance, there is limited published peer-reviewed evidence regarding the safety of administration during pregnancy of more recently licensed inactivated influenza vaccines products that are based on different vaccine technologies, including quadrivalent mammalian cell-culture-based vaccines (eg, Flucelvax Quad) and recombinant influenza vaccines (eg, Flublok, Supermix). Similarly, there is limited evidence regarding the safety of administration of influenza vaccine during the first trimester, specifically. Ongoing primary research in these areas is necessary, warranting future systematic review to inform guidance for healthcare providers counselling pregnant women about the benefits and safety of influenza vaccination.

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Acknowledgements We wish to thank Raymond Daniel for his consistently excellent support toward article retrieval and citation management throughout the review. We wish to acknowledge Matthew Tunis and Kelsey Young from the Public Health Agency of Canada for their input throughout the review.

Contributors CG and BH conceptualised the design and initial protocol for this study. DF, CH, ACT and DM provided feedback on the study protocol. BS designed and executed the literature search. DW, CG, CH, CB, MH, DBR, LE, AM, CS, MG and PAK were responsible for study selection and data collection. DW and BH performed and summarised findings from data analysis. DW and BH prepared the initial draft of the manuscript. All coauthors (DW, DF, CG, CH, CB, MH, NA, DBR, LE, AM, CS, MG, PAK, AS, BS, ACT, DM and BH) reviewed and approval the final draft of the manuscript. BH is guarantor of the review.

Funding This study was funded by the Canadian Institutes of Health Research and the Drug Safety and Effectiveness Network. ACT is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis.

Disclaimer The funders had no role in the design, analysis, interpretations or reporting of this research.

Competing interests BH has previously received honoraria from Eversana for methodologic advice related to the conduct of systematic reviews and meta-analysis. All remaining authors have no competing interests to declare.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All relevant data are provided within the manuscript and its supporting files. Our supplemental files include additional detail regarding the methods of our findings and we also have provided spreadsheets containing all of our gathered data.

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against influenza in cord blood and protection against laboratory-


