Supplementary material

This file contains the review supplementary material for the following manuscript: *Safety of influenza vaccination during pregnancy—a systematic review*. 2022. Authors: Dianna Wolfe, Deshayne Fell, Chantelle Garrity, Candycce Hamel, Claire Butler, Mona Hersi, Nadera Ahmadzai, Danielle Rice, Leila Esmaeilisaraji, Allan Michaud, Charlene Soobiah, Marco Ghassemi, Paul Khan, Angela Sinilaite, Becky Skidmore, Andrea Tricco, David Moher, Brian Hutton.

These materials consist of the following:

- Section 1: Protocol amendments
- Section 2: Detailed description of review methods
- Section 3: Literature search strategies
- Section 4: Risk of bias tools
- Section 5: Findings from non-prioritized outcomes for seasonal vaccines and non-standard outcome definitions for 2009 pandemic vaccines
- Section 6: Risk of bias plots
- Section 7: GRADE evidence profile table
- Section 8: Findings for monovalent 2009 pandemic influenza vaccine (2009 H1N1 MIV) vs placebo or no vaccine
- Section 9: Findings for studies including both TIV and 2009 pandemic vaccine
- Section 10: Findings for other pandemic influenza vaccines
- Section 11: Findings for other vaccine comparisons
- Section 12: Excluded studies list
- Section 13: Evidence maps
1. Protocol amendments

1) The review question was modified to include unborn children as well as women and newborns. This was to ensure that adverse birth outcomes were captured.

2) Several adjustments were made to clarify the study eligibility criteria presented in the protocol. These included excluding women vaccinated pre-conception or post-partum to comply with the review question (i.e., vaccinated at any time during pregnancy), exclusion of continuous outcome measures (e.g., birth weight), and exclusion of adverse event database studies as these are single-arm cohort studies, which were identified to be excluded in the protocol.

3) Where data were missing regarding vaccine details (e.g., valency, presence of adjuvant) and authors did not respond to emails, we inferred details based upon the vaccines known to be approved in the country of conduct at the time of the study. These methods have been outlined in the detailed description of the methods (Supplement Section 2).

4) Due to limitations of time and resources and the large number of observational studies included, risk of bias of observational studies was assessed using modifications of the Newcastle Ottawa Scale not ROBINS-I as reported in the protocol.

5) Due to a vast number of outcomes with differing definitions and time points of measure, we prioritized a small number for GRADE assessment, as per GRADE guidance.

6) Data from subgroup and sensitivity analyses reported in the included studies were extracted; however, due to sparsity of data, no syntheses could be conducted. The extracted data have been included in the data spreadsheets available in the repository.
2. Detailed description of review methods

The following subsections compliment the brief description of the review methods reported in the main text.

Literature search

An iterative process was used to develop search strategies by an experienced medical information specialist in consultation with the review team. The strategies reported here encompass both original review questions (i.e., vaccine efficacy/effectiveness studies were also sought). Prior to execution, a second senior information specialist used the PRESS Checklist\(^1\) to peer review the MEDLINE strategies. Separate strategies were performed for systematic reviews/meta-analyses, RCTs, and the remaining study designs. Systematic reviews were sought for background literature, not for inclusion, and RCTs were sought for the review question regarding vaccine efficacy that is not a part of this manuscript. Observational studies were sought in MEDLINE\(^*\) and Embase databases; however, the search results from all study designs were amalgamated, therefore, observational studies captured by searches for RCTs and reviews were also included. The RCT search was performed in Ovid MEDLINE\(^*\) ALL, Embase Classic+Embase, and the Cochrane Central Register of Controlled Trials. The following databases were searched for reviews, using the OVID platform: Ovid MEDLINE\(^*\) ALL, Embase Classic+Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment. All searches were performed on 11 December 2019, with an update to 3 June 2021.

A combination of controlled vocabulary (e.g., “Influenza, Human”, “Vaccination”, “Pregnant Women”) and keywords (e.g., “influenza”, “vaccine”, “pregnancy”) was used in the strategies. Research design filters were applied for systematic reviews/meta-analyses and RCTs, as appropriate, and syntax and vocabulary were adjusted across databases. No language or date restrictions were applied on any of the searches but animal-only records, opinion pieces and all but the most recent two years of conference abstracts were removed from search results, when possible.

The detailed search strategies are provided in Supplement Section 3. These strategies include the secondary review question regarding vaccine efficacy/effectiveness that is not a part of this manuscript. A grey literature search was conducted in June 2020 of clinical trial registries (clinicaltrials.gov and the International Clinical Trials Registry Platform), as well as a search guided by the Canadian Agency of Drugs and Technologies in Health (CADTH) Grey Matters Checklist\(^2\). Additional potentially relevant titles were also sought manually in the bibliographies of related systematic reviews and the final included studies.

Study selection process

Two levels of study selection were conducted: (1) titles and abstracts were screened initially for eligibility and (2) full texts of potentially relevant references were subsequently screened. A liberal accelerated approach was adopted to screen titles and abstracts, with one reviewer needed to include a reference and agreement of two reviewers to exclude. Conflicts at this level were not resolved but were promoted to full-text screening. Two reviewers screened full texts independently in duplicate, with conflicts...
resolution by discussion or consultation with a third reviewer. Screening and date management were operationalized by the online systematic review management software, DistillerSR® (Evidence Partners Inc., Ottawa, Canada). Prior to both stages of screening, forms were developed and piloted by the reviewers to maximize agreement and adjust wording of questions.

**Data collection**

Forms developed a priori in DistillerSR® were used to extract data. Initially, two reviewers piloted the forms on two references, and adjusted wording as required to improve extraction agreement. The eight-member review team subsequently piloted two to five references on each form to which they were assigned. One reviewer extracted data, which were subsequently verified by a second. Studies were categorized by study design (cohort or case-control) during initial extraction of study characteristics data. Subsequently, results data were extracted—including outcomes, interventions, comparators, and data—and captured on different forms for each study design. Authors were contacted where data were missing or methods were ambiguous (e.g., outcome definitions, vaccine types, statistical methods). If not reported in a study, we determined the presence or absence of adjuvant in pandemic influenza vaccines by identifying the formulation of vaccine(s) used in the country of conduct during the pandemic through cross-reference with other studies from the same country or through online sources (e.g., search of the US Food and Drug Administration drug approvals at https://www.accessdata.fda.gov/scripts/cder/daf/).

As well, where seasonal vaccine valency was not reported, we contacted authors for clarification, and if there was no response, we inferred valency by the approval date of quadrivalent vaccine in the country of conduct (e.g., approval of quadrivalent vaccines in the USA occurred prior to the 2012–13 influenza season3). Prior to the approval date, vaccines were assumed to be TIIV, and after the approval date, vaccines could be either TIIV or QIIV. Vaccines used during the 2009 H1N1 pandemic were considered monovalent (MIIV) unless reported otherwise. The data items extracted are summarized in Supplement Table 1.

We extracted results only for outcome definitions and follow-up periods of interest (e.g., congenital anomalies identified up to 6 months of age but not up to 12 months of age). Results reported by year or influenza season in multi-year studies were not extracted; we only extracted results for the entire study period.

**Supplement Table 1. Overview of data collection items**

<table>
<thead>
<tr>
<th>Study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, publication year, language, funding, conflicts of interest, study design, country where conducted, study years, influenza season(s), months of vaccine delivery, setting of administration, intervention details, method of gestational age measurement, inclusion and exclusion criteria, sample size</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographic data</th>
</tr>
</thead>
</table>
maternal age, race, comorbidities, key confounders reported, proportion vaccinated, gestational age at vaccination

### Results from cohort studies

- Intervention and comparator details; outcome definition, including when applicable, whether only full-term or only live births were measured and analyzed; timing of measurement relative to influenza season; group sizes and numbers of events; point estimate and 95% confidence interval; method(s) used to control for confounding; variables considered in confounding adjustment/matching/propensity score analyses

### Results from case-control studies

- Design (i.e., case-control or test-negative); case and control definitions, including when applicable, whether only full-term or only live births were measured and analyzed; exposure definition and window; timing of measurement relative to influenza season; group sizes and numbers of exposed; point estimate and 95% confidence interval; method(s) to control for confounding; variables considered in confounding adjustment/matching

### Risk of bias assessment

We used adaptations of the Newcastle-Ottawa Scale (NOS)\(^4\) to assess the risk of bias (ROB) in cohort and case-control studies. This scale captures potential biases commonly found in observational studies of the safety of influenza vaccines in pregnancy\(^5\)\(^6\). For each outcome, variables that are critical to control to reduce confounding bias were identified based on epidemiologic principles with our content expert (DF). Separate NOS guidance documents were developed iteratively for cohort and case-control studies separately through consultation with our content expert (see Supplement Section 4 for additional details). Risks of bias were assessed by outcome in all cohort and case-control studies by one reviewer (DW) who had developed the adapted NOS guidance. Training meetings were held for a team of reviewers prior to verification of data from each study design, to increase understanding of key concepts of the NOS tools. The team of reviewers then piloted the ROB forms and guidance on two references. Conflicts identified during ROB verification were resolved through consensus or discussion with either our content expert or a third reviewer.

Risk of bias summary plots were generated using the online robvis application (https://mcguinlu.shinyapps.io/robvis/\(^7\). Plots were stratified by vaccine type (i.e., TIIV, MIIV, and mixed vaccines) due to the large number of included studies and the prioritization of seasonal vaccines. Given that ROB was assessed for each reported outcome and that multiple outcomes were often reported that had differing risks of bias, in the summary plots, we included only the outcome identified as the primary outcome in the study methods or objective. Because observational studies are generally designed to minimize bias for primary outcomes, secondary outcomes may incur higher risks of bias (e.g., methods to reduce selection bias for the primary outcome may not reduce selection bias for secondary outcomes).
Many studies either reported numerous primary outcomes or did not specify any primary outcomes; therefore, we further stratified our ROB summary plots by the primary outcome in each study with (1) the lowest ROB and (2) the highest ROB. We did not summarize ROB by outcome, except in the process of assessment of level of evidence for prioritized outcomes. Raw data from ROB assessments for all outcomes are available in the supplementary data files.

**Synthesis and statistical methods**

Cleaning and collating of the extracted data were conducted for each study design, separately, in Microsoft Excel. Tables summarizing study characteristics were developed for cohort and case-control studies. Results data were tabulated by outcome to assess the feasibility of meta-analysis based on the availability of quantitative evidence and heterogeneity of comparisons, outcome definitions, and time points of measurement. When two or more studies reported findings for a given outcome definition, timepoint, and comparison and the extracted evidence was not clinically heterogeneous, we conducted pairwise meta-analyses using random effects models. We assessed statistical heterogeneity with the $I^2$ statistic, where values of $\geq 50\%$ suggested potentially important heterogeneity. Meta-analysis results were depicted on forest plots, with studies ordered by decreasing measure of effect.

Given the numerous interventions and comparators, the variety of outcome definitions and timepoints, and the inconsistent control of confounding bias and immortal time bias in studies, criteria were developed for inclusion in meta-analyses:

- **Interventions and comparators**: Our main meta-analyses focused on seasonal influenza vaccination administered at any time during pregnancy; syntheses of studies reporting pandemic influenza vaccination, combinations of seasonal and pandemic influenza vaccines, other pandemic vaccines, and comparisons of pandemic with pre-pandemic seasonal vaccines have been reported in Supplement Sections 8–11. Two outcomes required exposure windows different from “any time during pregnancy:” (1) because congenital anomalies generally develop in the first trimester, the exposure window of interest was the first trimester; (2) for spontaneous abortion, because it’s biologically plausible that recent exposure to a toxin may be associated with spontaneous abortion, the exposure windows of interest were within 28 days prior to the reference date or any time prior to the reference date. For pandemic vaccine studies, all comparators were amalgamated in MAs; for example, “no vaccine” could mean no influenza vaccine of any kind or no pandemic vaccine, but seasonal influenza vaccine may have been received. Many pandemic vaccine studies did not clarify if seasonal vaccination could have occurred.

- **Outcome definitions and timepoints**: Outcome definitions and timepoints recommended by the Brighton Collaboration were used to prioritize specific outcomes for meta-analysis (see “Assessment of level of evidence” below).

- **Confounding bias**: To minimize the effects of confounding in MAs, we only included studies that reported results adjusted for at least one covariate, whether by exclusion, matching, multivariable
modeling, or use of propensity score methods (e.g., inverse weighting, inclusion as a covariate, matching, stratification). Control of all key confounders (see ROB tools in Supplement Section 4) was not a criterion for inclusion.

- **Immortal time bias**: Analysis of time-dependent birth outcomes may be biased by immortal time, if exposure time is not accounted for through the use of Cox proportional hazards modelling or study design features. As well, a time-varying exposure variable should be used in models to account for greater probability of vaccination in longer pregnancies (e.g., women who give birth prematurely have a smaller window of opportunity for vaccination during pregnancy). For spontaneous abortion, preterm birth and stillbirth outcomes, where immortal time bias could substantially impact findings, we only pooled studies that had taken measures to reduce immortal time bias (although meta-analyses of studies that did not account for immortal time bias have been reported to demonstrate the effects of immortal time).

- **Effect estimates**: Different measures of effect were often reported in studies under consideration for meta-analysis. Given the rarity of our outcomes of interest (< 10% baseline risk) and the small effects of vaccination (e.g., effect sizes > 0.5 and < 2.0), we considered odds ratios (ORs) and risk ratios (RRs) to be equivalent. For similar reasons, hazard ratios (HRs) were considered approximate to RRs and ORs, due to the short follow-up periods of our studies (e.g., the duration of gestation) and the above criteria of rarity and small effects. Finally, HRs were also considered to approximate to IRRs. Pooled estimates from meta-analyses have been reported as HRs when all studies reported rate-based measures, and otherwise have been reported as RRs.

Descriptive summaries were developed for outcome definitions and timepoints that did not meet the Brighton Collaboration criteria (e.g., preterm birth measured at time points other than < 37 weeks). Similarly, studies reporting findings for a given time point or a given comparison, with no accompanying studies of the same design, were summarized descriptively due to limited evidence for the comparison. Descriptive summary was guided by the Synthesis without Meta-analysis (SwiM) statement and included a brief contextual description of the study or studies and their findings, as well as any elements of the study(ies) that may influence the interpretation of their data (e.g., study design, sample size, risk of bias) or be a source of heterogeneity. Where multiple studies were synthesized, they were grouped by study design and ordered by risk of bias (from low to high), and the range and distribution of their observed effects have been reported. Where possible, accompanying graphics (e.g., forest plots) demonstrating the reported estimates of effect provide a visual display of the evidence. We neither assessed certainty of findings nor formally investigated heterogeneity for any narrative summaries, beyond commenting on differences in study characteristics.

In forest plots, we have included columns of study- or outcome-level factors of interest that may influence effects (e.g., country of conduct, outcome definition, exposure window, follow-up with respect to the influenza season, ROB).

All analyses were conducted using Comprehensive Meta-Analysis software (Version 3.3.070, Biostat Inc., Englewood, NJ).
Assessment of level of the evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to assess the certainty of the evidence of the reported syntheses. Only outcomes identified as critical or important to decision making by our knowledge users and meeting other considerations outlined below received GRADE assessment:

1) Selecting and rating the importance of outcomes: Outcome definitions and timepoints extracted from the included studies were rated for importance in a prioritization exercise by the knowledge user working group. All outcome definitions were rated as critically or highly important and so other considerations were used to prioritize outcomes for GRADE assessment.

2) Outcome definition: As per protocol, maternal non-obstetric serious adverse events occurring during pregnancy were prioritized for GRADE assessment. For all birth outcomes, outcome definitions and timepoints of measurement were heterogeneous across the included studies. The following case definitions developed by the GAIA Network and Brighton Collaboration Network were used to aid in prioritization of birth outcome definitions:

a. Spontaneous abortion:
   i. High-income countries: fetal death before a cut-off between < 18 completed weeks to < 22 completed weeks (i.e., cut-off between 17 6/7 weeks and 21 6/7 weeks)
   ii. Low-income countries: fetal death before < 28 completed weeks (i.e., before 27 6/7 weeks) or an earlier cut-off, based on viability estimates for the country

b. Stillbirth:
   i. High-income countries: cut-off between SAB and stillbirth between 18 and 22 completed weeks or ≥ 500 g
   ii. Low-income countries: cut-off any week up to 28 completed weeks or ≥ 1000 g, based on viability estimates of the country

c. Preterm birth: < 37 weeks (i.e., 36 and 6/7 weeks or less OR < 259 days)

d. Small-for-gestational-age birth: weight below the 10th percentile of a valid reference standard/control group for gestational age and sex. A variety of international and country-specific reference scales are available, and the scale used (if cited) was assumed to be appropriate. Non-referenced scales were considered inappropriate.

e. Low birthweight: < 2,500 g, regardless of sex or gestational age at birth, measured at earliest timepoint, preferably within 48 hours of birth

f. Congenital anomalies (major): major functional or structural defects of prenatal origin; present at the time of live birth, fetal demise, or in utero; and diagnosed up to six months of age. Studies that included only live births were included but received downgraded risk of bias assessments.
3) Intervention and comparison:

a. Seasonal influenza vaccines (i.e., TIV or QIIV) were prioritized over monovalent pandemic vaccines or combinations of seasonal and monovalent pandemic vaccines (e.g., multi-year studies that included the 2009 H1N1 pandemic and years before and/or after). This consideration was based upon interest in currently used seasonal vaccines, whereas monovalent vaccines were of more general interest as lessons learned for the future.

b. Vaccination at any time during pregnancy was the primary exposure window of interest for all outcomes, except spontaneous abortion (within 28 days prior to event or any time prior to event) and congenital anomalies (first trimester vaccination).

4) Subgroup and sensitivity analyses: Subgroup and sensitivity analyses were not considered for GRADE assessment.

5) Other considerations:

a. Low birthweight: There is controversy regarding the utility of low birthweight, alone, as an outcome, given its association with gestational age at birth. As has been recommended, we prioritized the synthesis of studies reporting low birthweight in full-term infants only.

Using the online software GRADEpro GDT (https://gradepro.org/), we applied the GRADE framework to assess the strength and certainty of the evidence for each synthesis meeting the considerations above. Where meta-analysis was not possible, we assessed the body of evidence included in descriptive summaries. The body of evidence included in each synthesis was evaluated using the following domains: risk of bias, inconsistency, indirectness, and imprecision. Publication bias was only considered if 10 or more studies were included in the synthesis. Given that only observational studies were included, all syntheses were assigned a low certainty of evidence initially and were rated down or up accordingly. Rating up was considered only if no concerns were found in the above domains and one or more of the following was present: (1) a large magnitude of effect, (2) a dose-response gradient, or (3) no plausible residual confounders or biases that would reduce a demonstrated effect or suggest a spurious effect, when results showed no effect. A minimally contextualized approach was taken to rate the certainty of there being no difference between groups (i.e., relative effects were compared to a null effect of 1), rather than comparing to alternative thresholds.

In the main text, individual GRADE appraisals have been presented in text with the results of each synthesis, and a standard GRADE Summary of Findings (SoF) table has been provided, including lay statements as recommended by the GRADE Working Group. Lay statements project the certainty of the evidence (i.e., very low, low, moderate, high) as well as the magnitude of effect relative to a predetermined threshold (i.e., “no or trivial,” “small,” etc.), although magnitude of effect has no impact on wording for syntheses with a very low certainty of evidence. The magnitude of effect is based solely upon the point estimate and not on its associated confidence interval; therefore, lay statements may appear to imply that an intervention has a greater or lesser effect on an outcome than may be inferred when significance of the effect is also considered. Lack of statistical significance should not be
misinterpreted as having “no effect” in the context of GRADE evaluation. A GRADE Evidence Profile table has been provided in Supplement Section 7.

**Reporting**

The findings from the syntheses prioritized for GRADE assessment have been reported in the main manuscript, including salient subgroup or sensitivity analyses that may provide greater depth to inferences. Syntheses for monovalent 2009 H1N1 pandemic vaccine have been provided in Supplement Section 8. Also in Supplement Sections 5 and 9–11, we have reported findings for non-prioritized outcomes and non-standard outcome definitions; provided lists of studies that reported findings for (1) combined TIV and monovalent 2009 H1N1 pandemic vaccines, (2) other pandemic influenza vaccines, and (3) non-standard comparisons (e.g., comparisons of different seasonal influenza vaccines or adjuvants). All extracted data are available in the supplementary data sheets.

This review has been reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) statement and the SWiM statement for descriptive summaries. A completed PRISMA checklist is available with the main text.
3. Literature Search Strategies

The search strategies reported below encompass the entire original systematic review, with objectives to evaluated both safety and effectiveness/efficacy of influenza vaccination during pregnancy. Although RCTs were not included in the current safety review, their search strategies remain below because they were deduplicated with those of the observational studies, and some observational studies were identified from the RCT searches. Therefore, the individual search strategies could not be disentangled. A search update was later run to identify new evidence since the initial search conducted in December 2019.

Database: Embase Classic+Embase <1947 to 2019 December 09>, Ovid MEDLINE(R) ALL <1946 to December 09, 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <November 2019>

Search Strategy: RCTs

--------------------------------------------------------------------------------
1 Influenza, Human/ (72302)
2 (influenza* or flu or gripe).tw,kf. (282023)
3 exp Influenzavirus A/ (54965)
4 exp Influenzavirus B/ (5681)
5 (H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1).tw,kf. (57211)
6 or/1-5 [INFLUENZA] (296143)
7 exp Vaccination/ (264386)
8 Vaccines, Attenuated/ (27251)
9 Vaccines, Inactivated/ (11512)
10 ((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-valent) adj3 vaccin*).tw,kf. (72326)
11 ((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-valent) adj3 innoculat*).tw,kf. (5)
12 (immunis* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kf. (1634)
13 (immuniz* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kf. (21822)
14 (immunit* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kf. (14958)
15 (immunit* adj3 transfer*).tw,kf. (2945)
16 (immunit* adj3 maternally-acqui*).tw,kf. (44)
17 ((antibod* or anti-bod*) adj2 transfer*).tw,kf. (4104)
18 or/7-17 [VACCINATION] (357204)
19 6 and 18 [INFLUENZA VACCINATION] (50647)
20 Influenza, Human/[prevention & control] (21080)
21 Influenza Vaccines/ (53018)
22 ((influenza* or anti-influenza* or antiinfluenza* or flu or anti-flu or antiflu or gripe or anti-gripe or antigrippe) adj3 vaccin*).tw,kf. (56547)

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(((influenza* or anti-influenza* or antinfluenza* or flu or anti-flu or antiflu or grippe or anti-grippe or antigrippe) adj3 innoculat*).tw,kf. (3)

((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1) adj3 vaccin*).tw,kf. (7567)

((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1) adj3 innoculat*).tw,kf. (0)

((LAIV or "Q/LAIV") adj3 vaccin*).tw,kf. (1056)

((LAIV or "Q/LAIV") adj3 innoculat*).tw,kf. (0)

(adimFlu* or afluria or a-rix-tetra or adevac or adjupanrix or admune or aflunov or afluria or aggripal or agrippal or agriflu or alfa-rix or alfa-rix-tetra or allv3 or alorbat or alpha-rix or alpha-rix-tetra or anflu or arepanrix or batrevac or begripc or bevirvac or bvx m001 or cantgrip* or celtura or celvapan or cepas or chiroflu or chiromas or daronrix or enzira or flu immune or flu imune or flu-vac and flucol or fluad or fluarix or fluenz or flugen or flugene or fluviral or fluvirin or fluvirine or fluvirone or fluzone or focetria or focivia or "GC FLU" or gammaflu or "Green Flu-S" or grippol or grippovac or HNVAC or humenza or idflu or immugrip or imuvac or inleval or influavit or influel or influon or influvac or fluvax or vaccinum influenzae or vax102 or vaccinum influenzae or vaxiflu or vaginal flu or vaccinum influenzae or vaxiflu or "x-flu" or xanaflu or xanflu or xiv 3 or XIV 3 or TIV or QIV).tw,kf. (8227)

or/20-28 [INFLUENZA VACCINES] (84354)

19 or 29 [INFLUENZA VACCINATION/VACCINES] (93900)

exp Pregnancy/ (1682913)

Pregnancy Complications/ (101579)

Pregnancy Complications, Infectious/ (72097)

exp Pregnancy Trimesters/ (828400)

Pregnant Women/ (75617)

pregnан*.tw,kf. (1240031)

(prenatal* or pre-natal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum or gestational*).tw,kf. (684385)

maternal*.tw,kf. (605736)

exp Fetus/ (367654)

(fetus* or fetal* of foetus* or foetal*).tw,kf. (299361)

(fetomaternal* or feto-maternal* or foetomaternal* or foeto-maternal*).tw,kf. (8606)

Infectious Disease Transmission, Vertical/ (29504)

(vertical* adj3 transmi*).tw,kf. (17732)

(intrauterine or intra-uterine or "in utero").tw,kf. (199651)

(transplacent* or trans-placent* or uteroplacent* or utero-placent*).tw,kf. (23044)

exp Prenatal Diagnosis/ (181415)

Infants/ (795340)
(infant or infants or infancy or baby or babies).tw,kf. (1123434)
((one or two or three or four or five or six) adj (month or months) adj3 (age or aged or ages or old))).tw,kf. (32921)
(("1 month" or "2 month" or "2 months" or "3 month" or "3 months" or "4 month" or "4 months" or "5 month" or "5 months" or "6 month" or "6 months") adj3 (age or aged or ages or old))).tw,kf. (170648)
exp Infant, Newborn/.tw,kf. (1214118)
(neonat* or newborn? or new born?).tw,kf. (925299)
(SGA or LBW or VLBW).tw,kf. (37841)
small for gestational age.tw,kf. (23984)
low birth weight?.tw,kf. (65323)
or/31-55 (4759801)
30 and 56 [VACCINATION/VACCINE EXPOSURE IN PREGNANCY] (13481)
Prenatal Exposure Delayed Effects/ (50842)
delayed effect?.tw,kf. (5335)
((effect? or affect*) adj3 (offspring or off-spring)).tw,kf. (10675)
or/58-60 [PRENATAL EXPOSED DELAYED EFFECTS] (65456)
30 and 61 (67)
57 or 62 [VACCINATION/VACCINE EXPOSURE - PREGNANCY/PRENATAL] (13487)
exp Animals/ not Humans/ (17785022)
63 not 64 [ANIMAL-ONLY REMOVED] (10437)
(comment or editorial or news or newspaper article).pt. (2005975)
65 not 66 [OPINION PIECES REMOVED] (10150)
68 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt. (1156143)
clinical trials as topic/ (299182)
exp Randomized Controlled Trials as Topic/ (309932)
(randomized or random#ation? or randomly or RCT or placebo*).tw,kf. (3241698)
((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (665334)
trial.ti. (799266)
or/68-73 (4128758)
67 and 74 [RCTs] (2156)
76 75 use medall [MEDLINE RECORDS] (948)
influenza/ (115918)
exp influenza virus a/ (54965)
exp influenza virus b/ (5681)
exp influenza A/ (25707)
influenza B/ (2766)
pandemic influenza/ (4662)
seasonal influenza/ (5469)
(influenza* or flu or gripppe).tw,kw. (284006)
(H1N1 or PH1N1 or H3N2 or AH1N1 or "A[H1N1]" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1).tw,kw. (57523)
Influenza vaccination/ (234898)
inactivated vaccine/ (11512)
inactivated virus vaccine/ (3775)
live vaccine/ (15444)

((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-
valent) adj3 vaccin*).tw,kw. (72767)
((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-
valent) adj3 innoculat*).tw,kw. (5)

((immunis* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kw. (1652)
((immuniz* adj3 (active* or inactiv* or passive*)).tw,kw. (19270)

((immunit* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kw. (15066)
((immunit* adj3 transfer*).tw,kw. (2958)

((immunit* adj3 maternally-acqui*).tw,kw. (60)

((antibod* or anti-bod*) adj2 transfer*).tw,kw. (4142)

or/87-99 [VACCINATION] (338612)
86 and 100 [INFLUENZA VACCINATION] (52316)
influenza/pc [Prevention] (33758)
Influenza virus/pc [Prevention] (1)
pandemic influenza/pc [Prevention] (797)
seasonal influenza/pc [Prevention] (1492)
influenza vaccine/ (61069)

((influenza* or anti-influenza* or antiinfluenza* or flu or anti-flu or antiflu or grippe or anti-grippe
or antigrippe) adj3 vaccin*).tw,kw. (57229)

((influenza* or anti-influenza* or antiinfluenza* or flu or anti-flu or antiflu or grippe or anti-grippe
or antigrippe) adj3 innoculat*).tw,kw. (3)

((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2"
or H5N1) adj3 vaccin*).tw,kw. (7678)

((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2"
or H5N1) adj3 innoculat*).tw,kw. (0)

((LAIV or "Q/LAIV") adj3 vaccin*).tw,kw. (1068)

((LAIV or "Q/LAIV") adj3 innoculat*).tw,kw. (0)

(adimFlu* or afluria or a-rix-tetra or adevac or adjuvanrix or admune or aflunov or afluria or aggripal
or agripar or agriflu or alfa-rix or alfa-rix-tetra or allIV3 or alorbat or alpha-rix or alpha-rix-tetra or anflu
or arepanrix or batrevac or begripal or begrivac or bvx m001 or cantgrip* or celtura or celvapan or cepas
or chiroflu or chronixx or darorix or enzira or flu immune or flu imune or flu-vac or flud or fluarix or
fluarixteta or fluax or flublok or fluclavax or fluenz or flugen or flusiverse or flulaval or flumist
or fluogen or fluishield or flustat or fluvcinoc or fluv or fluvax or fluviral or fluvirin or fluvirine or fluviron
or fluzone or focetria or focliwia or "GC FLU" or gammaflu or "Green Flu-S" or grippol or gippovac or
HNVAC or humenza or idflu or immugrip or imuvac or inflexal or influject or influopenz or influorsplit or
influvac or intana or inviron-ol or invivac or iradogen or istivac or "M-001" or mastaflu or medi 3314 or
medi3314 or mf vject or "multimeric 001" or munevan or mutagrip or nivgrip or NASOVAC or optaflu or pandemrix or panenza or panful or panvax or pf 4522625 or pf4522625 or preflucel or prepandrix or previgrip or pumarix or sandovac or serinflu or skf 106160 or "split virion" or ultragrivac or utrix or vacciflu or vax 102 or vax102 or vaccinum influenzae or vaxifu or vaxigrip or vaxigrip tetra or vepacel or viroflu or "x-flu" or xanaflu or IVV3 or IIV4 or TIV or QIV).tw,kw. (8237)
114 or/102-113 [INFLUENZA VACCINES] (91031)
115 101 or 114 [INFLUENZA VACCINATION/VACCINES] (99991)
116 exp pregnancy/ (1682913)
117 exp pregnancy disorder/ (599741)
118 pregnant woman/ (88831)
119 pregnan*.tw,kw. (1252718)
120 (prenatal* or pre-natal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peripartum or peri partum or gestational*).tw,kw. (692489)
121 maternal*.tw,kw. (611587)
122 fetus/ (288285)
123 (fetus* or fetal* of foetus* or foetal*).tw,kw. (305396)
124 (fetomaternal* or feto-maternal* or foetomaternal* or foeto-maternal*).tw,kw. (8733)
125 vertical transmission/ (30315)
126 (vertical* adj3 transmi*).tw,kw. (18129)
127 (intrauterine or intra-uterine or "in utero").tw,kw. (201399)
128 (transplacent* or trans-placent* or uteroplacent* or utero-placent*).tw,kw. (23260)
129 prenatal exposure/ (52156)
130 exp prenatal diagnosis/ (181415)
131 exp infant/ (2278448)
132 (infant or infants or infancy or baby or babies).tw,kw. (1102457)
133 ((one or two or three or four or five or six) adj (month or months) adj3 (age or aged or ages or old)).tw,kw. (32928)
134 ("1 month" or "2 month" or "2 months" or "3 month" or "3 months" or "4 month" or "4 months" or "5 month" or "5 months" or "6 month" or "6 months") adj3 (age or aged or ages or old)).tw,kw. (170649)
135 (neonat* or newborn? or new born?).tw,kw. (923663)
136 (SGA or LBW or VLBW).tw,kw. (38086)
137 small for gestational age.tw,kw. (24403)
138 low birth weight?.tw,kw. (66707)
139 or/116-138 (5095940)
140 115 and 139 [VACCINATION/VACCINE EXPOSURE IN PREGNANCY] (15889)
141 prenatal exposure/ (52156)
142 delayed effect?.tw,kw. (5535)
143 ((effect? or affect*) adj3 (offspring or off-spring)).tw,kw. (10678)
144 fetus outcome/ (10794)
145 pregnancy outcome/ (107794)
146 or/141-143 [PRENATAL EXPOSED DELAYED EFFECTS] (66847)
147 115 and 146 (80)
148 140 or 147 [VACCINATION/VACCINE EXPOSURE - PREGNANCY/PRENATAL] (15893)
149 exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or
nonhuman/ or exp vertebrate/ (52167958)
150 exp human/ or exp human experimentation/ or exp human experiment/ (40375108)
151 149 not 150 (11794546)
152 148 not 151 [ANIMAL-ONLY REMOVED] (15299)
153 editorial.pt. (1145056)
154 152 not 153 [OPINION PIECES REMOVED] (15090)
155 exp randomized controlled trial/ or controlled clinical trial/ (1353973)
156 "clinical trial (topic)"/ or exp "controlled clinical trial (topic)"/ (273830)
157 (randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw. (3296353)
158 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (689652)
159 trial.ti. (799266)
160 or/155-159 (4116272)
161 154 and 160 [RCTs] (2744)
162 conference abstract.pt. (3662200)
163 161 not 162 (2671)
164 161 and 162 (73)
165 limit 164 to yr="2017-current" (18)
166 163 or 165 [MOST RECENT 2 YEARS CONFERENCE ABSTRACTS RETAINED] (2689)
167 166 use emczd [EMBASE RECORDS] (1100)
168 Influenza, Human/ (72302)
169 (influenza* or flu or grippe).ti,ab,kw. (283959)
170 exp Influenzavirus A/ (54965)
171 exp Influenzavirus B/ (5681)
172 (H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2"
or H5N1).ti,ab,kw. (57520)
173 or/168-172 [INFLUENZA] (297920)
174 exp Vaccination/ (264386)
175 Vaccines, Attenuated/ (27251)
176 Vaccines, Inactivated/ (11512)
177 ((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-
valent) adj3 vaccin*).ti,ab,kw. (72764)
178 ((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-
valent) adj3 innoculat*).ti,ab,kw. (5)
179 (immunis* adj3 (activ* or inactiv* or in-activ* or passive*)).ti,ab,kw. (1652)
180 (immuniz* adj3 (activ* or inactiv* or in-activ* or passive*)).ti,ab,kw. (22139)
181 (immunit* adj3 (activ* or inactiv* or in-activ* or passive*)).ti,ab,kw. (15066)
182 (immunit* adj3 transfer*).ti,ab,kw. (2958)
183 (immunit* adj3 maternally-acqui*).ti,ab,kw. (60)
184 ((antibod* or anti-bod*) adj2 transfer*).ti,ab,kw. (4142)
185 or/174-184 [VACCINATION] (357702)
(influenza* or anti-influenza* or anti-influenza* or flu or anti-flu or antiflu or grippe or anti-grippe or antigrippe) adj3 vaccin*.ti,ab,kw. (57220)

((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A/H3N2" or H5N1) adj3 vaccin*).ti,ab,kw. (7678)

((LAIV or "Q/LAIV") adj3 vaccin*).ti,ab,kw. (1068)

(adimFlu* or afluria or a-rix-tetra or adevac or adjuvanrix or admune or aflunov or afluria or agrigripal or agrigripal or agrigripal or alfa-rrix or alfa-rrix-tetra or allv3 or alorbat or alpha-rrix or alpha-rrix-tetra or anflu or arepanrix or batrevac or begri vac or bvx m001 or cantgrip* or celtura or selvapan or cepas or chiroflu or chiromas or daronrix or enzira or flu immune or flu imune or flu-vac or flud or flurax or fluarixtetra or fluax or flublok or flucelvax or fluenz or flugen or flugene or fluviral or fluvirine or fluvirine or fluviral or fluvirus or foetrix or fociivia or "GC FLU" or gammavir or "Green Flu-S" or grippol or grippovac or HNVAC or humenza or idflu or immugrip or imuvac or inflexal or influject or influpozzi or influsplit or influvac or intanza or inviren or invirex or invinac or iradogen or istivac or "M-001" or mafatul or mavi3314 or medi3314 or mfv ject or "multimeric 001" or munevan or mutagrip or nivgrip or NASOVAC or optafu or pandemrix or panenza or panful or panvax or pf 4522625 or pf4522625 or preflucel or prepanrix or previxgrip or pumarix or sandovac or serinflu or serlu or "split virion" or ultragrivac or ultrix or vacciflu or vaccinum influenzae or vax102 or vax102 or vax1102 or vaccinum influenzae or vaxflv or vaxflv or vaxflu or vaxflu or xanaflu or xiv3 or xiv4 or TIV or QIV).ti,ab,kw. (305396)

maternal*.ti,ab,kw. (611587)

fetomaternal* or feto-maternal* or foetomaternal* or foeto-maternal*).ti,ab,kw. (8733)

Infectious Disease Transmission, Vertical/ (29504)
(vertical* adj3 transmi*).ti,ab,kw. (18129)
(intrauterine or intra-uterine or "in utero").ti,ab,kw. (201399)
(transplacent* or trans-placent* or uteroplacent* or utero-placent*).ti,ab,kw. (23260)
exp Prenatal Diagnosis/ (181415)
Infants/ (795340)
(infant or infants or infancy or baby or babies).ti,ab,kw. (1102393)
((one or two or three or four or five or six) adj (month or months) adj3 (age or aged or ages or old)).ti,ab,kw. (32928)
exp Infant, Newborn/ (1214118)
(neonat* or newborn? or new born?).ti,ab,kw. (923644)
(SGA or LBW or VLBW).ti,ab,kw. (38043)
small for gestational age.ti,ab,kw. (24403)
low birth weight?.ti,ab,kw. (66707)
or/198-222 (4778924)
197 and 223 [VACCINATION/VACCINE EXPOSURE IN PREGNANCY] (13613)
exp Prenatal Exposure Delayed Effects/ (50842)
delayed effect?.ti,ab,kw. (5535)
((effect? or affect*) adj3 (offspring or off-spring)).ti,ab,kw. (10678)
or/225-227 [PRENATAL EXPOSED DELAYED EFFECTS] (65572)
197 and 228 (67)
224 or 229 [VACCINATION/VACCINE EXPOSURE - PREGNANCY/PRENATAL] (13618)
conference abstract.pt. (3662200)
230 not 231 (12928)
230 and 231 (690)
limit 233 to yr="2017-current" (153)
232 or 234 [MOST RECENT 2 YEARS CONFERENCE ABSTRACTS RETAINED] (13081)
235 use cc[central records] (1030)
236 76 or 167 or 236 [ALL DATABASES] (3078)
remove duplicates from 237 (1832)
238 use medall (938)
238 use emczd (517)
238 use ctr (377)

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Database: Embase Classic+Embase <1947 to 2019 December 10>, Ovid MEDLINE(R) ALL <1946 to December 10, 2019>

Search Strategy:

1. Influenza, Human/ (70044)
2. (influenza* or flu or grippe).tw,kf. (273490)
3. exp Influenzavirus A/ (54103)
4. exp Influenzavirus B/ (5405)
5. (H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1).tw,kf. (55636)
6. or/1-5 [INFLUENZA] (287526)
7. exp Vaccination/ (262030)
8. Vaccines, Attenuated/ (26550)
9. Vaccines, Inactivated/ (10933)
10. ((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-valent) adj3 vaccin*).tw,kf. (68167)
11. ((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-valent or quadrivalent or quadri-valent) adj3 innoculat*).tw,kf. (5)
12. (immunis* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kf. (1567)
13. (immuniz* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kf. (21395)
14. (immunit* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kf. (14743)
15. (immunit* adj3 transfer*).tw,kf. (2928)
16. (immunit* adj3 maternally-acqui*).tw,kf. (44)
17. ((antibod* or anti-bod*) adj2 transfer*).tw,kf. (4033)
18. or/7-17 [VACCINATION] (350408)
19. 6 and 18 [INFLUENZA VACCINATION] (48390)
20. Influenza, Human(pc [prevention & control] (21080)
21. Influenza Vaccines/ (51551)
22. ((influenza* or anti-influenza* or antinfluenza* or flu or anti-flu or antiflu or gripe or anti-gripe or antigripe) adj3 vaccin*).tw,kf. (52586)
23. ((influenza* or anti-influenza* or antiinfluenza* or flu or anti-flu or antiflu or gripe or anti-gripe or antigripe) adj3 innoculat*).tw,kf. (3)
24. ((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1) adj3 vaccin*).tw,kf. (6849)
25. ((H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1) adj3 innoculat*).tw,kf. (0)
26. ((Q/LAIV) adj3 vaccin*).tw,kf. (942)
27. ((Q/LAIV) adj3 innoculat*).tw,kf. (0)
28. (adimFlu* or afluria or a-rix-tetra or adevac or adjupanrix or admune or aflunov or afluria or aggripal or agrippal or agriflu or alfa-rix or alfa-rix-tetra or allV3 or alorbat or alpha-rix or alpha-rix-tetra or anflu
or arepanrix or batrevac or begripal or begrivac or bx m001 or cantgrip* or celtura or celvapan or cepas or chiroflu or chiromas or daronrix or enzira or flu immune or flu imune or flu-vac or fluid or fluvarix or fluarixtetra or fluxax or flublok or fluceleka or fluenz or flugen or flugen or flugene or flulavial or flumist or flugon or fluxed or flushtar or fluvarcinol or fluvax or fluvarial or fluvirin or fluvirine or fluvir or fluzone or focolia or "GC FLU" or gammaflu or "Green Flu-S" or gippol or gippovac or HNVAC or humenza or idflu or immugrip or imuvac or inflexal or influject or influpozzi or influsplit or influvac or intanza or inviron-ol or invivac or iradogen or istivac or "M-001" or mastaflu or medi3314 or medi3314 or mfvject or "multimeric 001" or munevan or mutagrip or nivgrip or NASOVAC or optaflu or pandemrix or panenza or panvax or pf 4522625 or pf4522625 or preflucel or prepandrix or prevgrip or pumarix or sandovac or serinflu or skf 106160 or "split virion" or ultragrip or ultrix or vacciflu or vax 102 or vax102 or vaccinum influenzae or vaxiflu or vaxigrip or vaxigriptetra or vepacel or viroflu or "x-flu" or xanafiu or IIV3 or IIV4 or IV or IIV4 or QIV).tw,kf. (7219)
29 or/20-28 [INFLUENZA VACCINES] (80160)
30 19 or 29 [INFLUENZA VACCINATION/VACCINES] (89489)
31 exp Pregnancy/ (1662655)
32 Pregnancy Complications/ (100067)
33 Pregnancy Complications, Infectious/ (71303)
34 exp Pregnancy Trimesters/ (826821)
35 Pregnant Women/ (75423)
36 pregnan*.tw,kf. (1191647)
37 (prenatal* or pre-natal* or antenatal* or ante natal* or antepartum or ante partum or perinatal* or peri natal* or peri partum or peri partum or gestational*).tw,kf. (662236)
38 maternal*.tw,kf. (588044)
39 exp Fetus/ (366033)
40 (fetus* or fetal* of foetus* or foetal*).tw,kf. (295552)
41 (fetomaternal* or feto-maternal* or foetomaternal* or foeto-maternal*).tw,kf. (8498)
42 Infectious Disease Transmission, Vertical/ (29005)
43 (vertical* adj3 transmi*).tw,kf. (17551)
44 (intrauterine or intra-uterine or "in utero").tw,kf. (193275)
45 (transplacent* or trans-placent* or uteroplacent* or utero-placent*).tw,kf. (22725)
46 exp Prenatal Diagnosis/ (180660)
47 Infants/ (774636)
48 (infant or infants or infancy or baby or babies).tw,kf. (1083306)
49 (one or two or three or four or five or six) adj (month or months) adj3 (age or aged or ages or old)).tw,kf. (31809)
50 ("1 month" or "2 month" or "2 months" or "3 month" or "3 months" or "4 month" or "4 months" or "5 month" or "5 months" or "6 month" or "6 months") adj3 (age or aged or ages or old)).tw,kf. (162980)
51 exp Infant, Newborn/ (1199331)
52 (neonat* or newborn? or new born?).tw,kf. (900478)
53 (SGA or LBW or VLBW).tw,kf. (35565)
54 small for gestational age.tw,kf. (23144)
55 low birth weight?.tw,kf. (61688)
56  or/31-55 (4639224)
57  30 and 56 [VACCINATION/VACCINE EXPOSURE IN PREGNANCY] (12518)
58  Prenatal Exposure Delayed Effects/ (50519)
59  delayed effect?.tw,kf. (5128)
60  ((effect? or affect*) adj3 (offspring or off-spring)).tw,kf. (10541)
61  or/58-60 [PRENATAL EXPOSURE DELAYED EFFECTS] (64806)
62  30 and 61 (66)
63  57 or 62 [VACCINATION/VACCINE EXPOSURE - PREGNANCY/PRENATAL] (12524)
64  exp Animals/ not Humans/ (17785585)
65  63 not 64 [ANIMAL-ONLY REMOVED] (9474)
66  (comment or editorial or news or newspaper article).pt. (2003691)
67  65 not 66 [OPINION PIECES REMOVED] (9187)
68  systematic review.pt. (117387)
69  exp systematic reviews as topic/ (26990)
70  meta analysis.pt. (107982)
71  exp meta-analysis as topic/ (59346)
72  (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf. (381388)
73  (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs).tw,kf. (455100)
74  exp Technology assessment, biomedical/ (24702)
75  (cochrane or health technology assessment or evidence report or systematic reviews).jw. (45914)
76  (network adj (MA or MAs)).tw,kf. (24)
77  (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kf. (17124)
78  indirect* compar*.tw,kf. (5220)
79  (indirect treatment* adj1 compar*).tw,kf. (800)
80  (mixed treatment* adj1 compar*).tw,kf. (1304)
81  (multiple treatment* adj1 compar*).tw,kf. (369)
82  (multi-treatment* adj1 compar*).tw,kf. (6)
83  simultaneous* compar*.tw,kf. (2313)
84  mixed comparison?.tw,kf. (68)
85  or/68-84 (797379)
86  67 and 85 [SYSTEMATIC REVIEWS] (264)
87  (controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt. (584917)
88  clinical trials as topic/ (265995)
89  exp Randomized Controlled Trials as Topic/ (302258)
90  (randomified or randomi#ation? or randomly or RCT or placebo*).tw,kf. (2281978)
91  ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (406207)
trial.ti. (503466)
or/87-92 (2955758)
67 and 93 [RCTs] (1342)
67 not (86 or 94) [RECORDS OTHER THAN REVIEWS AND RCTS] (7707)
95 use medall [MEDLINE RECORDS] (4964)
influenza/ (113660)
exp influenzavirus a/ (54103)
exp influenzavirus b/ (5405)
exp influenza A/ (25710)
influenza B/ (2767)
pandemic influenza/ (4662)
seasonal influenza/ (5472)
(influenza* or flu or grippe).tw,kw. (274630)
(H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A/H3N2" or "A/H3N2" or H5N1).tw,kw. (55911)
or/97-105 [INFLUENZA] (302378)
vaccination/ (232569)
influenza vaccination/ (16524)
inactivated vaccine/ (10933)
inactivated virus vaccine/ (3775)
live vaccine/ (15445)
((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-Valent or quadrivalent or quadrivalent) adj3 vaccin*).tw,kw. (68561)
((activ* or attenuat* or live or inactiv* or in-activ* or trivalent or tri-Valent or quadrivalent or quadrivalent) adj3 innoculat*).tw,kw. (5)
(immunis* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kw. (1585)
(immuniz* adj3 (active* or inactiv* or passive*)).tw,kw. (18779)
(immunit* adj3 (activ* or inactiv* or in-activ* or passive*)).tw,kw. (14798)
(immunit* adj3 transfer*).tw,kw. (2940)
(immunit* adj3 maternally-acqui*).tw,kw. (60)
((antibod* or anti-bod*) adj2 transfer*).tw,kw. (4069)
or/107-119 [VACCINATION] (331850)
106 and 120 [INFLUENZA VACCINATION] (50071)
influenza/pc [Prevention] (33758)
Influenza virus/pc [Prevention] (1)
pandemic influenza/pc [Prevention] (797)
seasonal influenza/pc [Prevention] (1492)
influenza vaccine/ (59602)
((influenza* or anti-influenza* or antiinfluenza* or flu or anti-flu or antiflu or grippe or anti-grippe or antigrippe) adj3 vaccin*).tw,kw. (53184)
((influenza* or anti-influenza* or antiinfluenza* or flu or anti-flu or antiflu or grippe or anti-grippe or antigrippe) adj3 innoculat*).tw,kw. (3)
[H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1] adj3 vaccin*.tw,kw. (6940)

(H1N1 or PH1N1 or H3N2 or AH1N1 or "A(H1N1)" or "A/H1N1" or AH3N2 or "A(H3N2)" or "A/H3N2" or H5N1) adj3 innoculat*.tw,kw. (0)

(LAIV or "Q/LAIV") adj3 vaccin*.tw,kw. (954)

(LAIV or "Q/LAIV") adj3 innoculat*.tw,kw. (0)

(adimFlu* or afluria or a-rix-tetra or adevac or adjupanrix or admune or aflunov or afluria or aggrippal or agrippal or agrippal or alfa-rix or alfa-rix-tetra or allV3 or alorbat or alpha-rix or alpha-rix-tetra or anflu or arepanrix or batrevac or begripal or begrixvac or bvl m001 or cantgrip* or celtura or celvapan or cepas or chiroflu or chiromas or daronrix or enzira or flu immune or flu vac or flu vac or fluorix or fluax or flublok or flucelvax or fluenz or flugen or flugin or flugene or flugene or fluvirine or fluvirine or fluvirine or fluvirine or fluzone or focetria or foclivia or "GC FLU" or gammaflu or "Green Flu-S" or grippol or grippovac or HNVAC or humenza or idflu or immugrip or imuvac or inflexal or inflixact or influenza or fluflu or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or influenza or 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(neonat* or newborn? or new born?).tw,kw. (897304)
(SGA or LBW or VLBW).tw,kw. (35809)
small for gestational age.tw,kw. (23563)
low birth weight?.tw,kw. (62640)
or/136-158 (4971237)
135 and 159 [VACCINATION/VACCINE EXPOSURE IN PREGNANCY] (14865)
prenatal exposure/ (51833)
delayed effect?.tw,kw. (5328)
((effect? or affect*) adj3 (offspring or off-spring)).tw,kw. (10544)
fetus outcome/ (10795)
pregnancy outcome/ (104983)
or/161-163 [PRENATAL EXPOSED DELAYED EFFECTS] (66196)
135 and 166 (79)
160 or 167 [VACCINATION/VACCINE EXPOSURE - PREGNANCY/PRENATAL] (14869)
exp animal/ or exp animal experimentation/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (51600261)
exp human/ or exp human experimentation/ or exp human experiment/ (39806483)
169 not 170 (11795474)
168 not 171 [ANIMAL-ONLY REMOVED] (14275)
editorial.pt. (1144822)
174 172 not 173 [OPINION PIECES REMOVED] (14066)
meta-analysis/ (284472)
"systematic review"/ (343749)
"meta analysis (topic)"/ (40812)
"systematic review (topic)"/ (24166)
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biomedical technology assessment/ (23590)
(cochrane or health technology assessment or evidence report).jw. (39702)
(network adj (MA or MAs)).tw,kw. (24)
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indirect* compar*.tw,kw. (5295)
(indirect treatment* adj1 compar*).tw,kw. (805)
(mixed treatment* adj1 compar*).tw,kw. (1326)
(multiple treatment* adj1 compar*).tw,kw. (375)
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simultaneous* compar*.tw,kw. (2313)
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or/175-191 (866745)
174 and 192 [SYSTEMATIC REVIEWS] (492)
conference abstract.pt. (3645704)
193 not 194 (466)
193 and 194 (26)
limit 196 to yr="2017-current" (15)
195 or 197 [MOST RECENT 2 YRS CONFERENCE ABSTRACTS RETAINED] (481)
exp randomized controlled trial/ or controlled clinical trial/ (1353985)
"clinical trial (topic)"/ or exp "controlled clinical trial (topic)"/ (273929)
(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw. (2284171)
(trial.ti. (503466)
or/199-203 (3046959)
174 and 204 [RCTs] (1989)
205 not 194 (1917)
205 and 194 (72)
limit 207 to yr="2017-current" (17)
206 or 207 [MOST RECENT 2 YEARS CONFERENCE ABSTRACTS RETAINED] (1989)
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210 and 194 (599)
limit 212 to yr="2017-current" (131)
211 or 213 [MOST RECENT 2 YEARS CONFERENCE ABSTRACTS RETAINED] (11341)
214 use emczd [EMBASE RECORDS] (6151)
96 or 215 [BOTH DATABASES] (11115)
limit 216 to yr="2011-current" (5570)
remove duplicates from 217 (3860)
216 not 217 (5545)
remove duplicates from 219 (4034)
218 or 220 (7894)
221 use medall (4917)
221 use emczd (2977)
4. Risk of bias (ROB) tools

**ROB Appraisal of Cohort studies: Newcastle Ottawa Scale**

*Note:* a study could be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars could be awarded for Comparability.

**Selection**

![](image)

**Representativeness of the Exposed Cohort**

This item is assessing the representativeness of the exposed (vaccinated) women to the community (i.e., study’s target population), not the representativeness of the sample of women to some general population or to the systematic review currently being conducted. Some influenza studies report their target population (e.g., Navajo/Apache women in the American Southwest, women in their second and third trimester). However, most do not and it’s left to the reader to determine whether the study setting and sample are generalizable (external validity). We will not critically appraise external validity, unless the publication reports that their sample did not represent their target.

**What to think about:** Let’s assume that the source of the sample (the sampling frame) adequately reflects the target population for the study (external validity). Does the study also have internal validity? In other words, are the findings derived from the study sample likely to be the same as the true findings had the entire sampling frame been selected? The sampling frame may be a national database, a regional database, all women attending a prenatal clinic in a defined period, all infants born at selected hospitals over a defined period, etc. The entire sampling frame may be selected for a study, as in some retrospective cohort database studies, or a sample of women/infants within the sampling frame may be selected. A study’s sampling strategy can bias the study’s findings so they deviate from the truth (selection bias).

Selection bias occurs when the probability of selection into a study is influenced by exposure or disease status. For instance, if the disease status of a potential participant influences their decision to participate in the study (or their likelihood of being selected, in retrospective studies), selection bias may be present. For example, in a cohort study of the effect of influenza vaccination on birth outcomes, women were
recruited immediately after delivery and outcome and exposure data retrospectively ascertained. Due to psychological impacts, women who had experienced any negative birth outcome (i.e., stillbirth, congenital anomalies, etc.) were less likely to participate than women with healthy newborns, regardless of their vaccination history. Thus, the probability of participation was associated with some birth outcomes. In the 2x2 tables below, women who participated are represented in yellow, and the proportion of yellow in each cell of the sampling frame is the probability of participation (sampling fraction). If there is no selection bias (left panel), the probabilities of participation in cells a and b are equal and the probabilities of participation in cells c and d are equal. In our example, to obtain the same sample size, more women in cells b and d would have to be recruited. Therefore, the probability of participation in cell a < cell b and the probability of participation in cell c < cell d, and selection bias is present for some birth outcomes (right panel).

<table>
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<tr>
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Another common example of a selection bias is the exclusion of stillborn infants and fetal deaths from analyses of congenital anomalies. Because congenital anomalies generally develop in the first trimester, stillborn infants and fetuses aborted after the first trimester should be assessed for congenital anomalies and not excluded from the sample. The sampling fractions for this example are depicted in the right panel of the figure below. All sampling fractions will decrease as stillbirths are removed from the study sample and put back in the sampling frame; however, more stillbirths would have been associated with the D+ column, therefore, the proportion of pregnancies included in cells a and c would decrease more than that in cells b and d. Once again, the probability of selection in cell a < cell b and the probability of selection in cell c < cell d, thus selection bias is present for the congenital anomalies outcome.
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<tbody>
<tr>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
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Q1: Is the exposed cohort representative of the average vaccinated pregnant woman or newborn infant in the sampling frame?

a) Truly or somewhat representative of the average pregnant woman or newborn infant in the community: **STAR**

b) The exposed cohort was not representative of the average pregnant woman or newborn infant in the community: **NO STAR**

c) A group of the exposed women was selected non-randomly (e.g., volunteers): **NO STAR**

d) No description of the derivation of the cohort: **NO STAR**

**Selection of the Non-Exposed Cohort**

The non-exposed cohort should be recruited from the same source as the exposed cohort, otherwise, the two groups may vary substantially in unmeasured confounding factors. If influenza outcomes were measured, the non-exposed cohort should also be recruited at the same time as the exposed cohort. That said, for pandemic studies, selection of a cohort of women immediately prior to the pandemic is a valid non-exposed cohort because outcomes are unlikely to vary with time.

**For H1N1 (monovalent) vaccine studies,** the study design must have accounted for access to vaccination. H1N1 vaccine became available at different times in different countries, usually around Oct/Nov 2009. Because we are only interested in vaccination *during pregnancy,* all women in the sample must have had access to the vaccine during pregnancy, and so they must have delivered *after* the vaccine became available.

Q2: How was the unexposed cohort selected?

a) Drawn from the same community (and time for influenza outcomes) as the exposed cohort: **STAR**

b) Drawn from a different source (or time for influenza outcomes): **NO STAR**

c) No description of the derivation of the non-exposed cohort: **NO STAR**
**Ascertainment of Exposure**

The exposure status of the participants should be ascertained through methods that are not subject to recall bias. As well, there should be no potential for misclassification bias (e.g., vaccination may or may not have been recorded in the medical record, meaning some apparently non-exposed women were truly exposed). Exposure misclassification that is not dependent on the outcome (i.e., non-differential) usually biases the effect estimate toward the null and will be considered to have no impact. Misclassification that is dependent on the outcome can have varying effects on the effect estimate.

Q3: How was exposure status ascertained?

a) Secure record (e.g., medical records, national vaccine database), with no misclassification or with non-differential misclassification: STAR

b) Structured interview by blinded investigator OR written self-report conducted before the outcome occurs: STAR

c) Structured interview (blinded or non-blinded) OR written self-report conducted after the outcome occurs: NO STAR

d) There is potential differential misclassification of exposure regardless of type of ascertainment: NO STAR

e) No description: NO STAR

**Demonstration that the Outcome of Interest was not Present at the Start of Study (or Before Exposure Occurred for Exposed Participants)**

The participant must have been at risk for the outcome of interest at the start of the follow-up period.

For influenza outcomes, studies should have demonstrated that the mother had no history of influenza during the current influenza season prior her enrollment. Infants are newly born and so could not have had influenza (give a star for all infant influenza outcomes).

For post-natal infant mortality outcomes in retrospective cohort studies, investigators must have said that they selected liveborn infants.

Congenital anomalies occur during first trimester; therefore, vaccination during the first trimester is the only valid exposure for this outcome and any women vaccinated in the second or third trimester should be defined as unexposed.

Spontaneous abortion and preterm birth both have defined at-risk periods during gestation. Vaccination after the at-risk period should be defined as unexposed.

Q4: Did the study demonstrate that the outcome of interest was not present at the start of the study (or before exposure had occurred for exposed participants)?
a) Yes: STAR  
b) No: NO STAR

**Comparability**

Comparability of Cohorts on the Basis of the Design or the Analysis

A maximum of two stars can be allotted in this category. One or more of the following methods to control for confounding must have been used: (1) matching: exposed and unexposed individuals were matched on key confounders or on propensity scores that included all key confounders, (2) exclusion: individuals with key confounders were excluded from the study, or (3) analytical adjustment: key confounders were controlled for in the analysis, through adjustment of individual confounders, adjustment of propensity scores, stratification, or use of other methods such as splines. ***Statements of no differences in key confounders between exposure groups or that differences were not statistically significant in key confounders are not sufficient for establishing comparability (i.e., a lack of confounding).***

If analytically adjusted through consideration as covariates in a multivariable model, key confounders must have been at least considered as potential confounders in the early stages of analysis, but may not have been included in a final model, if (a) in univariable models they were found not to have a significant association with either the exposure or the outcome, OR (b) they were included in a propensity score model and found not to be significant, OR (c) they were included as individual covariates in a multivariable model and were found not to impact the point estimate of the exposure variable substantially (i.e., by more than a prespecified value like 10–20%). Although confounders should be considered in the context of a causal diagram that demonstrates the relationships of all measured and unmeasured potential confounders to the exposure and outcome of interest (Hernan 2002), we are not requiring this to have been done.

**Intervening and collider variables:** Studies using analytical adjustment (not propensity scores) and controlling an intervening variable lose a star (i.e., a variable that occurs temporally between exposure and outcome and is statistically associated with both). See causal diagram below.

**Collinearity:** We will not consider inclusion of potentially collinear variables in models as a bias. For example, if a propensity score is developed with a large number of variables without evaluating collinearity, we will not consider this a bias.

**Key confounders (by type of outcome):**

*All birth outcomes and congenital anomalies up to 6 months of age:* maternal age, smoking status during pregnancy, socioeconomic status (may include education, income, employment, measures of neighbourhood SES, etc.)

*Infant influenza outcomes:* timing of birth with respect to the influenza season, socioeconomic status
**Infant death (early and later):** timing of birth with respect to the influenza season (while influenza may not cause significant infant death, RSV does and circulates at the same time), maternal age, smoking status during pregnancy, socioeconomic status

**Maternal influenza outcomes:** maternal age, smoking status during study period, socioeconomic status (see above), pre-existing co-morbid conditions as defined by the study

Q5: Regarding confounders, the study...

a) ...considered (see above) and/or controlled for confounders in some way and controlled all key confounders for the outcome in the list above: **TWO STARS**

b) ...considered and/or controlled for confounders but did not control all key confounders for the outcome: **ONE STAR**

c) ...controlled for an intervening variable as a covariate (see below): **MINUS ONE STAR**

d) ...did not control for any biologically or epidemiologically plausible confounders: **NO STARS**

**A simple confounder**

\[ C \rightarrow E \rightarrow D \]

C occurs temporally before the Exposure and is associated with both the Exposure and the Disease. An example of this would be E = influenza vaccine, D = lab-confirmed influenza, and C = timing of birth with respect to the influenza season. In studies of infant lab-confirmed influenza, the timing of birth must be considered: births may be excluded based on their timing relative to the influenza season, analyses may be stratified by influenza season, or a time-varying covariate for the influenza season should be included in survival analyses.

**Intervening variable**

\[ E \rightarrow C \rightarrow D \]

C occurs temporally between the Exposure and the Disease (intervening variable). An unmeasured variable with associations with the intervening variable and the outcome has also been shown. An example of this would be E = influenza vaccine, D = infant lab-confirmed influenza, and C = preterm birth (ignore U). If influenza vaccination is assumed to be associated with preterm birth, preterm birth should not be included as a confounder because it is associated with both E and D and occurs temporally between them. (That said, no association between vaccination and preterm birth has been conclusively found to date, this is just an example.)

(Diagrams from Hernan 2002)

**Outcome**

**Assessment of Outcome**

Outcomes must have been adequately assessed to establish their occurrence. For lab-confirmed influenza, vaccine efficacy, and lab-confirmed influenza hospitalization, influenza must have been
confirmed by a test with an acceptably high specificity (e.g., RT-PCR, indirect or direct immunofluorescence assay). For most other outcomes, reference to the medical record or linkage to a database is sufficient to satisfy the requirement for confirmation of the event. For immediate maternal non-obstetric SAEs, observation by outcome assessor is sufficient, while for SAEs defined as requiring hospitalization, hospital records are sufficient.

Self-report of all outcomes is insufficient, without confirmation by medical records or independent blind assessment by an outcome assessor. However, for small-for-gestational age, which is calculated from the estimated date of conception, women’s self-report of their last menstrual period (LMP) is sufficient to estimate date of conception.

Q6: Was assessment of the outcome sufficient to minimize misclassification of the outcome?

a) Independent blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (e.g., medical records, birth registry): STAR

b) Record linkage (e.g., identified through ICD codes on database records): STAR

c) Self-report (i.e., no reference to original medical records or x-rays to confirm the outcome): NO STAR

d) No description: NO STAR.

Was Follow-up Long Enough for Outcomes to Occur?

Minimum follow-up time by outcome:

- Maternal influenza/VE/ILI: no minimum follow-up...the 14-day window after vaccination should be considered unexposed, but we’re not considering that during ROB assessments

- Child influenza/VE/hospitalization/ILI: no minimum follow-up, although preferable to 6 months of age. See comment above regarding 14-day window post-vaccination.

- Stillbirths: followed mothers to delivery (20–42 gestational weeks)

- Spontaneous abortion: followed mothers up to 20 gestational weeks

- Maternal SAEs: immediate: at least 30 minutes post-vaccination. Otherwise, no minimum follow-up time

- Maternal death/mortality: no minimum follow-up

- Preterm birth: followed mothers up to 37 gestational weeks or delivery, whichever is first

- Small-for-gestational age: followed mothers to delivery or 42 gestational weeks, whichever is first

- Low birthweight: followed mothers to delivery or 42 gestational weeks, whichever is first
- Congenital anomalies: no minimum follow-up
- Early neonatal death (within 7 days of birth): up to 7 days or as defined by the study
- Death within 6 months of birth: preferably followed to 6 months of age, although we’ve extracted some death outcomes that had shorter follow-up and were documented as such

Q7: Was the minimum follow-up time met for the outcome?
   a) Yes: STAR
   b) No: NO STAR

**Adequacy of Follow-up**

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome. If 1–10% losses were reported but balance between groups was not reported, please speculate whether the losses were likely related to either the exposure or the outcome rather than broadly not awarding a star for non-reporting.

Q8: Were losses to follow-up minimal and balanced?
   a) Complete follow-up (all subjects accounted for): STAR
   b) Subjects lost to follow-up unlikely to introduce bias
      i. very small numbers lost (<1%) and proportion is much lower than the outcome event rate/risk, regardless of balance between groups and reasons for loss, OR
      ii. small number lost (1–10%) and balanced between exposure groups. A description should be provided of reasons for losses (although not mandatory), and losses should be unrelated to the outcome or exposure (see guidance above): STAR
   c) Any other description of numbers lost, balance, and reasons for losses: NO STAR
   d) No statement: NO STAR

**ROB Appraisal of Case-control studies: Newcastle Ottawa Scale for Cohort Studies**

Note: a study could be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars could be awarded for Comparability.
**Selection**

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**Target population**

**Sampling frame**

**Sample**

**Representativeness of the Exposed Cohort**

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**What to think about**: Let’s assume that the source of the sample (the sampling frame) adequately reflects the target population for the study (external validity). Does the study also have internal validity? In other words, are the findings derived from the study sample likely to be the same as the true findings had the entire sampling frame been selected? The sampling frame may be a national database, a regional database, all women attending a prenatal clinic in a defined period, all infants born at selected hospitals over a defined period, etc. The entire sampling frame may be selected for a study, as in some retrospective cohort database studies, or a sample of women/infants within the sampling frame may be selected. A study’s sampling strategy can bias the study’s findings so they deviate from the truth (selection bias).

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of participation in cells $c$ and $d$ are equal. In our example, to obtain the same sample size, more women in cells $b$ and $d$ would have to be recruited. Therefore, the probability of participation in cell $a \prec cell b$ and the probability of participation in cell $c \prec cell d$, and selection bias is present for some birth outcomes (right panel).

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</tbody>
</table>

Another common example of a selection bias is the exclusion of stillborn infants and fetal deaths from analyses of congenital anomalies. Because congenital anomalies generally develop in the first trimester, stillborn infants and fetuses aborted after the first trimester should be assessed for congenital anomalies and not excluded from the sample. The sampling fractions for this example are depicted in the right panel of the figure below. All sampling fractions will decrease as stillbirths are removed from the study sample and put back in the sampling frame; however, more stillbirths would have been associated with the D+ column, therefore, the proportion of pregnancies included in cells $a$ and $c$ would decrease more than that in cells $b$ and $d$. Once again, the probability of selection in cell $a \prec cell b$ and the probability of selection in cell $c \prec cell d$, thus selection bias is present for the congenital anomalies outcome.

<table>
<thead>
<tr>
<th>No selection bias present</th>
<th>Selection bias present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D+</strong></td>
<td><strong>D+</strong></td>
</tr>
<tr>
<td><strong>E+</strong></td>
<td><strong>E+</strong></td>
</tr>
<tr>
<td><strong>E-</strong></td>
<td><strong>E-</strong></td>
</tr>
</tbody>
</table>

Q1: Is the exposed cohort representative of the average vaccinated pregnant woman or newborn infant in the sampling frame?
e) Truly or somewhat representative of the average pregnant woman or newborn infant in the community: **STAR**

f) The exposed cohort was not representative of the average pregnant woman or newborn infant in the community: **NO STAR**

g) A group of the exposed women was selected non-randomly (e.g., volunteers): **NO STAR**

h) No description of the derivation of the cohort: **NO STAR**

**Selection of the Non-Exposed Cohort**
The non-exposed cohort should be recruited from the same source as the exposed cohort, otherwise, the two groups may vary substantially in unmeasured confounding factors. If influenza outcomes were measured, the non-exposed cohort should also be recruited at the same time as the exposed cohort. That said, for pandemic studies, selection of a cohort of women immediately prior to the pandemic is a valid non-exposed cohort because outcomes are unlikely to vary with time.

**For H1N1 (monovalent) vaccine studies**, the study design must have accounted for access to vaccination. H1N1 vaccine became available at different times in different countries, usually around Oct/Nov 2009. Because we are only interested in vaccination *during pregnancy*, all women in the sample must have had access to the vaccine during pregnancy, and so they must have delivered *after* the vaccine became available.

Q2: How was the unexposed cohort selected?

d) Drawn from the same community (and time for influenza outcomes) as the exposed cohort: **STAR**

e) Drawn from a different source (or time for influenza outcomes): **NO STAR**

f) No description of the derivation of the non-exposed cohort: **NO STAR**

**Ascertainment of Exposure**
The exposure status of the participants should be ascertained through methods that are not subject to recall bias. As well, there should be no potential for misclassification bias (e.g., vaccination may or may not have been recorded in the medical record, meaning some apparently non-exposed women were truly exposed). Exposure misclassification that is not dependent on the outcome (i.e., non-differential) usually biases the effect estimate toward the null and will be considered to have no impact. Misclassification that is dependent on the outcome can have varying effects on the effect estimate.

Q3: How was exposure status ascertained?

f) Secure record (e.g., medical records, national vaccine database), with no misclassification or with non-differential misclassification: **STAR**

g) Structured interview by blinded investigator OR written self-report conducted *before the outcome occurs*: **STAR**
h) Structured interview (blinded or non-blinded) OR written self-report conducted after the outcome occurs: NO STAR

i) There is potential differential misclassification of exposure regardless of type of ascertainment: NO STAR

j) No description: NO STAR

**Demonstration that the Outcome of Interest was not Present at the Start of Study (or Before Exposure Occurred for Exposed Participants)**

The participant must have been at risk for the outcome of interest at the start of the follow-up period.

*For influenza outcomes*, studies should have demonstrated that the mother had no history of influenza during the current influenza season prior her enrollment. Infants are newly born and so could not have had influenza (give a star for all infant influenza outcomes).

*For post-natal infant mortality outcomes* in retrospective cohort studies, investigators must have said that they selected liveborn infants.

*Congenital anomalies* occur during first trimester; therefore, vaccination during the first trimester is the only valid exposure for this outcome and any women vaccinated in the second or third trimester should be defined as unexposed.

*Spontaneous abortion and preterm birth* both have defined at-risk periods during gestation. Vaccination after the at-risk period should be defined as unexposed.

Q4: Did the study demonstrate that the outcome of interest was not present at the start of the study (or before exposure had occurred for exposed participants)?

   c) Yes: STAR

   d) No: NO STAR

**Comparability**

Comparability of Cohorts on the Basis of the Design or the Analysis

A maximum of two stars can be allotted in this category. One or more of the following methods to control for confounding must have been used: (1) **matching**: exposed and unexposed individuals were matched on key confounders or on propensity scores that included all key confounders, (2) **exclusion**: individuals with key confounders were excluded from the study, or (3) **analytical adjustment**: key confounders were controlled for in the analysis, through adjustment of individual confounders, adjustment of propensity scores, stratification, or use of other methods such as splines. ***Statements of no differences in key confounders between exposure groups or that differences were not statistically significant in key confounders are not sufficient for establishing comparability (i.e., a lack of confounding).***
If analytically adjusted through consideration as covariates in a multivariable model, key confounders must have been at least considered as potential confounders in the early stages of analysis, but may not have been included in a final model, if (a) in univariable models they were found not to have a significant association with either the exposure or the outcome, OR (b) they were included in a propensity score model and found not to be significant, OR (c) they were included as individual covariates in a multivariable model and were found not to impact the point estimate of the exposure variable substantially (i.e., by more than a prespecified value like 10–20%). Although confounders should be considered in the context of a causal diagram that demonstrates the relationships of all measured and unmeasured potential confounders to the exposure and outcome of interest (Hernan 2002), we are not requiring this to have been done.

Intervening and collider variables: Studies using analytical adjustment (not propensity scores) and controlling an intervening variable lose a star (i.e., a variable that occurs temporally between exposure and outcome and is statistically associated with both). See causal diagram below.

Collinearity: We will not consider inclusion of potentially collinear variables in models as a bias. For example, if a propensity score is developed with a large number of variables without evaluating collinearity, we will not consider this a bias.

Key confounders (by type of outcome):

All birth outcomes and congenital anomalies up to 6 months of age: maternal age, smoking status during pregnancy, socioeconomic status (may include education, income, employment, measures of neighbourhood SES, etc.)

Infant influenza outcomes: timing of birth with respect to the influenza season, socioeconomic status

Infant death (early and later): timing of birth with respect to the influenza season (while influenza may not cause significant infant death, RSV does and circulates at the same time), maternal age, smoking status during pregnancy, socioeconomic status

Maternal influenza outcomes: maternal age, smoking status during study period, socioeconomic status (see above), pre-existing co-morbid conditions as defined by the study

Q5: Regarding confounders, the study...

e) ...considered (see above) and/or controlled for confounders in some way and controlled all key confounders for the outcome in the list above: TWO STARS

f) ...considered and/or controlled for confounders but did not control all key confounders for the outcome: ONE STAR

g) ...controlled for an intervening variable as a covariate (see below): MINUS ONE STAR

h) ...did not control for any biologically or epidemiologically plausible confounders: NO STARS
A simple confounder

C occurs temporally before the Exposure and is associated with both the Exposure and the Disease. An example of this would be E = influenza vaccine, D = lab-confirmed influenza, and C = timing of birth with respect to the influenza season. In studies of infant lab-confirmed influenza, the timing of birth must be considered: births may be excluded based on their timing relative to the influenza season, analyses may be stratified by influenza season, or a time-varying covariate for the influenza season should be included in survival analyses.

Intervening variable

C occurs temporally between the Exposure and the Disease (intervening variable). An unmeasured variable with associations with the intervening variable and the outcome has also been shown. An example of this would be E = influenza vaccine, D = infant lab-confirmed influenza, and C = preterm birth (ignore U). If influenza vaccination is assumed to be associated with preterm birth, preterm birth should not be included as a confounder because it is associated with both E and D and occurs temporally between them. (That said, no association between vaccination and preterm birth has been conclusively found to date, this is just an example.)

(Diagrams from Hernan 2002)

Outcome

Assessment of Outcome

Outcomes must have been adequately assessed to establish their occurrence. For lab-confirmed influenza, vaccine efficacy, and lab-confirmed influenza hospitalization, influenza must have been confirmed by a test with an acceptably high specificity (e.g., RT-PCR, indirect or direct immunofluorescence assay). For most other outcomes, reference to the medical record or linkage to a database is sufficient to satisfy the requirement for confirmation of the event. For immediate maternal non-obstetric SAEs, observation by outcome assessor is sufficient, while for SAEs defined as requiring hospitalization, hospital records are sufficient.

Self-report of all outcomes is insufficient, without confirmation by medical records or independent blind assessment by an outcome assessor. However, for small-for-gestational age, which is calculated from the estimated date of conception, women’s self-report of their last menstrual period (LMP) is sufficient to estimate date of conception.

Q6: Was assessment of the outcome sufficient to minimize misclassification of the outcome?

e) Independent blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (e.g., medical records, birth registry): STAR

f) Record linkage (e.g., identified through ICD codes on database records): STAR
g) Self-report (i.e., no reference to original medical records or x-rays to confirm the outcome): **NO STAR**

h) No description: **NO STAR.**

**Was Follow-up Long Enough for Outcomes to Occur?**

**Minimum follow-up time by outcome:**

- Maternal influenza/VE/ILI: no minimum follow-up...the 14-day window after vaccination should be considered unexposed, but we’re not considering that during ROB assessments
- Child influenza/VE/hospitalization/ILI: no minimum follow-up, although preferable to 6 months of age. See comment above regarding 14-day window post-vaccination.
- Stillbirths: followed mothers to delivery (20–42 gestational weeks)
- Spontaneous abortion: followed mothers up to 20 gestational weeks
- Maternal SAEs: immediate: at least 30 minutes post-vaccination. Otherwise, no minimum follow-up time
- Maternal death/mortality: no minimum follow-up
- Preterm birth: followed mothers up to 37 gestational weeks or delivery, whichever is first
- Small-for-gestational age: followed mothers to delivery or 42 gestational weeks, whichever is first
- Low birthweight: followed mothers to delivery or 42 gestational weeks, whichever is first
- Congenital anomalies: no minimum follow-up
- Early neonatal death (within 7 days of birth): up to 7 days or as defined by the study
- Death within 6 months of birth: preferably followed to 6 months of age, although we’ve extracted some death outcomes that had shorter follow-up and were documented as such

Q7: Was the minimum follow-up time met for the outcome?

c) Yes: **STAR**

d) No: **NO STAR**

**Adequacy of Follow-up**

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome. If 1–10% losses were reported but balance between groups was not reported, please speculate whether the losses were likely related to either the exposure or the outcome rather than broadly not awarding a star for non-reporting.
Q8: Were losses to follow-up minimal and balanced?

e) Complete follow-up (all subjects accounted for): **STAR**

f) Subjects lost to follow-up unlikely to introduce bias

   i. very small numbers lost (<1%) and proportion is much lower than the outcome event rate/risk, regardless of balance between groups and reasons for loss, OR

   ii. small number lost (1–10%) and balanced between exposure groups. A description should be provided of reasons for losses (although not mandatory), and losses should be unrelated to the outcome or exposure (see guidance above): **STAR**

g) Any other description of numbers lost, balance, and reasons for losses: **NO STAR**

h) No statement: **NO STAR**
5. Findings for non-prioritized outcomes and non-standard outcome definitions for seasonal influenza vaccination

Low birth weight

Four studies\(^4\)\(^8\)\(^5\)\(^4\)\(^8\)\(^5\)\(^8\)\(^10\)\(^4\) reported adjusted analyses for low birthweight (< 2,500 g); however, only three studies\(^5\)\(^8\)\(^5\)\(^8\)\(^10\)\(^4\) reported the subgroup of full-term infants and were included in the prioritized synthesis.

**Prioritized synthesis**

When the three studies\(^5\)\(^8\)\(^5\)\(^8\)\(^10\)\(^4\) were pooled, a small protective effect of TIIIV on low birthweight in full-term infants was found that was not statistically significant (aRR = 0.74, 95% CI = 0.52–1.05; \(I^2 = 29.52\); **Figure 13**). The certainty of evidence was assessed to be very low, given concerns regarding imprecision. Two of the three studies\(^5\)\(^8\)\(^5\)\(^8\) were conducted in the same population during different time periods, using similar methods, and had very similar results. The third study\(^10\) was smaller, used a time-varying exposure, and appeared to include both stillborn and live-born infants, whereas the other studies did not. This study found a moderate protective effect of vaccination that was significant. Because only full-term infants were included in the included analyses, immortal time bias was considered to be reduced. GRADE lay statement: “The evidence is very uncertain about the effect of seasonal influenza vaccine during pregnancy on the occurrence of low birthweight (< 2,500 g) [very low certainty of evidence].”

**Figure 13. Meta-analysis of observational studies reporting low birth weight (< 2,500 g) in live- or stillborn full-term infants, comparing TIIIV to no vaccine**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Data on Season?</th>
<th>Time of observation</th>
<th>Birth status</th>
<th>ROB</th>
<th>Data type</th>
<th>Effect estimate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Events / Birth</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohamed et al., 2020</td>
<td>Australia</td>
<td>No</td>
<td>Full</td>
<td>All</td>
<td>7</td>
<td>aHR</td>
<td>0.38</td>
<td>0.19</td>
<td>0.60</td>
<td>51 / 159</td>
<td>36 / 107</td>
<td>14.77</td>
</tr>
<tr>
<td>Dodds et al., 2012</td>
<td>Canada</td>
<td>No</td>
<td>Full</td>
<td>Low</td>
<td>8</td>
<td>aOR</td>
<td>0.80</td>
<td>0.52</td>
<td>1.13</td>
<td>28 / 1764</td>
<td>100 / 8820</td>
<td>41.85</td>
</tr>
<tr>
<td>Legger et al., 2014</td>
<td>Canada</td>
<td>No</td>
<td>Full</td>
<td>Low</td>
<td>8</td>
<td>aOR</td>
<td>0.85</td>
<td>0.56</td>
<td>1.39</td>
<td>25 / 1801</td>
<td>123 / 7130</td>
<td>45.46</td>
</tr>
</tbody>
</table>

aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CI = confidence interval; ROB = risk of bias; TIIIV = trivalent inactivated influenza vaccine; vax = vaccine

Preterm birth

A recently published cohort study in South Africa found a significant protective effect of seasonal influenza vaccination on PTB; however, immortal time bias was not accounted for and the statistical methods were insufficiently reported to allow extraction of a valid effect estimate. When a small sample of primigravid women were analysed, the protective effect was not statistically significant.
**Spontaneous abortion**

One study reported an exposure window of 1–14 gestational weeks (first trimester vaccination) and enrolment before 20 gestational weeks. A small harmful effect was reported, similar to that found with an exposure window up to 20 gestational weeks (aHR = 1.12, 95% CI = 0.47–2.65).

A cohort study from Japan reported raw data for SAB under 22 gestational weeks by exposure group. Both vaccinated and unvaccinated women had a 0.4% risk of SAB following first trimester vaccination.
Figure 14. Meta-analysis of observational studies reporting low birth weight (<2,500 g), whether liveborn or stillborn, comparing 2009 pandemic vaccine given at any time during pregnancy to no pandemic vaccine and stratified by gestational age at birth (full term vs other ages; adjusted analyses only)

<table>
<thead>
<tr>
<th>Full term only?</th>
<th>Study name</th>
<th>Country</th>
<th>Adjuvanted?</th>
<th>ROB</th>
<th>Gestational age</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Events / Total</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rubindaim et al., 2013</td>
<td>Argentina</td>
<td>Yes</td>
<td>7</td>
<td>&gt;22 weeks</td>
<td>0.74</td>
<td>0.65</td>
<td>0.84</td>
<td>357 / 7293</td>
<td>1606 / 23195</td>
<td>17.68</td>
</tr>
<tr>
<td></td>
<td>Hetikinen et al., 2012</td>
<td>The Netherlands</td>
<td>Yes</td>
<td>6</td>
<td>Any</td>
<td>0.76</td>
<td>0.53</td>
<td>1.09</td>
<td>64 / 2310</td>
<td>68 / 2212</td>
<td>7.51</td>
</tr>
<tr>
<td></td>
<td>Richards et al., 2015</td>
<td>US</td>
<td>No</td>
<td>7</td>
<td>&gt;26 weeks</td>
<td>0.79</td>
<td>0.56</td>
<td>1.11</td>
<td>66 / 1064</td>
<td>132 / 1505</td>
<td>8.16</td>
</tr>
<tr>
<td></td>
<td>Huang et al., 2014 S/T</td>
<td>Taiwan</td>
<td>Both</td>
<td>7</td>
<td>Any</td>
<td>0.81</td>
<td>0.74</td>
<td>0.88</td>
<td>608 / 7955</td>
<td>8001 / 84782</td>
<td>19.37</td>
</tr>
<tr>
<td></td>
<td>Ludvigsson et al., 2013</td>
<td>Sweden</td>
<td>Yes</td>
<td>9</td>
<td>Any</td>
<td>0.91</td>
<td>0.79</td>
<td>1.04</td>
<td>1337 / 13297</td>
<td>301 / 7790</td>
<td>16.89</td>
</tr>
<tr>
<td></td>
<td>Baum et al., 2015</td>
<td>Finland</td>
<td>Yes</td>
<td>9</td>
<td>&gt;24 weeks</td>
<td>1.05</td>
<td>0.91</td>
<td>1.22</td>
<td>628 / 34241</td>
<td>236 / 9363</td>
<td>16.34</td>
</tr>
<tr>
<td></td>
<td>Posinovuk et al., 2012</td>
<td>Denmark</td>
<td>Yes</td>
<td>8</td>
<td>Any</td>
<td>1.14</td>
<td>0.94</td>
<td>1.38</td>
<td>225 / 6642</td>
<td>199 / 6642</td>
<td>14.05</td>
</tr>
<tr>
<td>Yes</td>
<td>Häberg et al., 2013</td>
<td>Norway</td>
<td>Yes</td>
<td>8</td>
<td>Full</td>
<td>0.90</td>
<td>0.75</td>
<td>1.07</td>
<td>NR / NR</td>
<td>NR / NR</td>
<td>73.02</td>
</tr>
<tr>
<td></td>
<td>Fabiani et al., 2015</td>
<td>Italy</td>
<td>Yes</td>
<td>8</td>
<td>Full</td>
<td>0.91</td>
<td>0.69</td>
<td>1.23</td>
<td>47 / 1883</td>
<td>2624 / 92121</td>
<td>26.98</td>
</tr>
</tbody>
</table>

CI = confidence interval; MIV = monovalent influenza vaccine; NR = not reported; ROB = risk of bias; vax = vaccine
Numbers followed by plus signs (+) are lower than the total number included in the meta-analysis due to unreported raw data.
Stillbirth

A single cohort study reported adjusted findings and accounted for immortal time bias; however, details of its statistical methods were not reported sufficiently to allow extraction of an effect estimate and it could not be pooled in the meta-analysis reported in the main text. A non-significant association between seasonal influenza vaccination and stillbirth was found (p = 0.08)\(^{106}\).

Three studies reporting unadjusted results\(^{49, 59, 105}\) found protective effects of TIV administered at any time during pregnancy on stillbirth, but statistical significance was inconsistent (Figure 15). In the same studies, inconsistent effects with wide confidence intervals were found when the effect of first trimester seasonal influenza vaccination was evaluated (Figure 15).

**Figure 15.** Findings from cohort studies comparing seasonal influenza vaccine to no vaccine that reported stillbirth as an outcome and reported unadjusted results. Stratified by timing of exposure.

<table>
<thead>
<tr>
<th>Trimester of exposure</th>
<th>Only during flu season?</th>
<th>Study</th>
<th>Country</th>
<th>ROB</th>
<th>Risk ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>TIV</th>
<th>No vac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>No</td>
<td>Chambers et al., 2016</td>
<td>USA</td>
<td>5</td>
<td>0.38</td>
<td>0.05</td>
<td>2.92</td>
<td>2 / 1249</td>
<td>2 / 1407</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sheffield et al., 2012</td>
<td>USA</td>
<td>7</td>
<td>0.60</td>
<td>0.41</td>
<td>0.88</td>
<td>30 / 8884</td>
<td>436 / 76819</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Ohtsuki et al., 2020</td>
<td>Japan</td>
<td>5</td>
<td>0.44</td>
<td>0.12</td>
<td>1.58</td>
<td>3 / 3943</td>
<td>11 / 6387</td>
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<tr>
<td>First</td>
<td>No</td>
<td>Chambers et al., 2016</td>
<td>USA</td>
<td>5</td>
<td>0.98</td>
<td>0.13</td>
<td>7.50</td>
<td>2 / 477</td>
<td>2 / 407</td>
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<td></td>
<td></td>
<td>Sheffield et al., 2012</td>
<td>USA</td>
<td>7</td>
<td>2.54</td>
<td>0.36</td>
<td>18.01</td>
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<td>NR / 76919</td>
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<tr>
<td></td>
<td>Yes</td>
<td>Ohtsuki et al., 2020</td>
<td>Japan</td>
<td>5</td>
<td>0.30</td>
<td>0.01</td>
<td>6.33</td>
<td>0 / 1121</td>
<td>2 / 1705</td>
</tr>
</tbody>
</table>

Other outcomes

Findings for numerous other outcomes for which data were extracted are not presented in the main manuscript or in the above sections. These outcomes include all non-standard outcome definitions/timings for both seasonal and pandemic vaccines. Please refer to the supplemental Excel spreadsheets for these findings.
6. Risk of bias plots

ROB summary plots for studies evaluating 2009 pandemic H1N1 vaccine

Few pandemic vaccine studies adjusted appropriately for confounding (~25–30%). Losses due to follow-up (or poor reporting of losses) was also a source of ROB in many studies (25–40%).

**Figure 1. ROB summary plots for observational studies evaluating 2009 pandemic vaccine (MIIV), including lowest ROB primary outcomes (Panel A) and highest ROB primary outcomes**

<table>
<thead>
<tr>
<th>Panel A</th>
<th>Selection bias 1</th>
<th>Selection bias 2</th>
<th>Selection bias 3</th>
<th>Selection bias 4</th>
<th>Comparability bias</th>
<th>Outcome/Exposure bias 1</th>
<th>Outcome/Exposure bias 2</th>
<th>Outcome/Exposure bias 3</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

**Panel B**

<table>
<thead>
<tr>
<th>Selection bias 1</th>
<th>Selection bias 2</th>
<th>Selection bias 3</th>
<th>Selection bias 4</th>
<th>Comparability bias</th>
<th>Outcome/Exposure bias 1</th>
<th>Outcome/Exposure bias 2</th>
<th>Outcome/Exposure bias 3</th>
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</tr>
</tbody>
</table>

CC = case-control; NOS = Newcastle Ottawa Scale; QIV = quadrivalent inactivated influenza vaccine; ROB = risk of bias; TIV = trivalent inactivated influenza vaccine

NOS stars awarded were converted to the judgments “low,” “some concerns,” and “high” as per the legend.

Selection bias 1: Representativeness of the exposed women (cohort studies) or cases (CC studies)
Selection bias 2: Selection of non-exposed women (cohort studies) or controls (CC studies)
Selection bias 3: Adequate ascertainment of exposure (cohort studies) or case definition (CC studies)
Selection bias 4: Outcome could not occur before exposure (cohort studies) or adequate control definition (CC studies)
Comparability bias: Appropriate adjustment for confounding
ROB summary plots for studies evaluating combinations of TIIV and 2009 pandemic vaccine, other influenza vaccines or non-standard comparisons

Twelve observational studies were included in the figures below. Four studies were multi-year studies encompassing the 2009 pandemic, combining pre- and/or post-pandemic seasonal vaccines with 2009 pandemic vaccines as the exposed cohort. Three studies evaluated 2009 pandemic vaccines, with or without 2009–10 seasonal vaccine, one study evaluated a vaccine from a previous pandemic (n = 1), and one study compared 2009 pandemic vaccine to a pre-pandemic cohort of women who received seasonal influenza vaccination.

Few studies were judged to have an overall low risk of bias (20–40%), with moderate to high ROB frequently judged for exposure ascertainment, adjustment for confounders, and losses to follow-up.

Study-level ROB plots

All observational studies evaluating either TIIV/QIIV (Figure 4) or 2009 pandemic vaccine (Figure 5) received a low or moderate overall judgement of ROB, indicating that the score cut-offs used for the NOS tool may not be overly sensitive to identify studies with high ROB. Studies could receive no stars in half of the domains (5 out of 9 stars), and yet still be determined to have only “some concerns” regarding overall risk of bias. Twenty-one of 29 studies (72%) evaluating seasonal influenza vaccine received a judgement of low overall ROB, and 18 of 24 studies (75%) evaluating 2009 pandemic vaccine received a judgement of low overall ROB, when the primary outcome with the lowest ROB for each study was considered.

Most studies in Figure combined seasonal and 2009 pandemic vaccines as the exposed cohort, however, one study evaluated a monovalent vaccine used in a previous pandemic (Deinard et al. 1981), and one study compared 2009 pandemic vaccine to seasonal influenza vaccination prior to the 2009 pandemic (Conlin et al., 2013).

Fewer observational studies evaluating a combination of seasonal and 2009 pandemic vaccines were judged to have a low overall ROB (6 of 12 studies (50%)) than studies evaluating seasonal (72%) or pandemic vaccines (75%) alone. The two studies that evaluated either another pandemic vaccine or compared 2009 pandemic vaccine to seasonal vaccine were all judged to have a moderate or high overall ROB.
**Figure 2. ROB summary plots for observational studies evaluating other influenza vaccines or non-standard comparisons, including lowest ROB primary outcomes (Panel A) and highest ROB primary outcomes**

**Panel A**

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Low 1*/2/20 stars</th>
<th>Some concerns: 10 stars</th>
<th>High 5 stars</th>
<th>No Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Low 1*/2/20 stars</th>
<th>Some concerns: 10 stars</th>
<th>High 5 stars</th>
<th>No Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Panel B**

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Low 1*/2/20 stars</th>
<th>Some concerns: 10 stars</th>
<th>High 5 stars</th>
<th>No Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Low 1*/2/20 stars</th>
<th>Some concerns: 10 stars</th>
<th>High 5 stars</th>
<th>No Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CC = case-control; NOS = Newcastle Ottawa Scale; QIIV = quadrivalent inactivated influenza vaccine; ROB = risk of bias; TIIV = trivalent inactivated influenza vaccine

NOS stars awarded were converted to the judgments “low,” “some concerns,” and “high” as per the legend.

Selection bias 1: Representativeness of the exposed women (cohort studies) or cases (CC studies)
Selection bias 2: Selection of non-exposed women (cohort studies) or controls (CC studies)
Selection bias 3: Adequate ascertainment of exposure (cohort studies) or case definition (CC studies)
Selection bias 4: Outcome could not occur before exposure (cohort studies) or adequate control definition (CC studies)
Comparability bias: Appropriate adjustment for confounding
Outcome/Exposure bias 1: Adequate assessment of outcome (cohort studies) or ascertainment of exposure (CC studies)
Outcome/Exposure bias 2: Adequate follow-up time for outcome to occur (cohort studies) or the same ascertainment of exposure was used for both cases and controls (CC studies)
Outcome/Exposure bias 3: Losses to follow-up (cohort studies) or non-response in exposure ascertainment (CC studies)
Figure 4. Study-level ROB assessment results for observational studies evaluating seasonal influenza vaccine (TIIV or QIIV), including primary outcomes with lowest ROB and highest ROB.

<table>
<thead>
<tr>
<th>Study</th>
<th>Low ROB primary outcome</th>
<th>High ROB primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td>McMorow et al., 2020</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mohammed et al., 2020</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Oluji et al., 2020</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Panagiotakopoulos et al., 2020</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sproake et al., 2020</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Donahue et al., 2019</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>McHugh et al., 2019a</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>McHugh et al., 2019b</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Singh et al., 2019</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oluji et al., 2018</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Avila et al., 2017</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Donahue et al., 2017</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>McHugh et al., 2017</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Zerba et al., 2017</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chambers et al., 2016</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Louik et al., 2016</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olsen et al., 2016</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ragas et al., 2016c</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Ahmed et al., 2014</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Legge et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nordin et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aledare et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Irving et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nordin et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dudds et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sheffield et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Omer et al., 2011</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Munoz et al., 2006</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Black et al., 2004</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Legend:
- D1: Representativeness of exposed/cases
- D2: Selection of non-exposed/controls
- D3: Ascertainment of exposure/Case definition adequate
- D4: Demonstration that outcome was not present prior to exposure/Control definition adequate
- D5: Comparability of cohorts/cases and controls
- D6: Assessment of outcome-Assessment of exposure
- D7: Follow-up long enough for outcome to occur/fails exposure assignment for cases and controls
- D8: Losses to follow-up/Non-response in exposure assignment

Judgment:
- High (D-3 stars)
- Satisfactory (2-5 stars)
- Low (1-5 stars)
- No information
**Figure 5. Study-level ROB assessment results for observational studies evaluating 2009 H1N1 pandemic vaccine, including primary outcomes with lowest ROB and highest ROB.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Low ROB primary outcome</th>
<th>High ROB primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 D2 D3 D4 D5 D6 D7 D8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ludwigsson et al., 2016</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Vazquez-Benitez et al., 2016</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Baum et al., 2015</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coenders et al., 2015</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fabbri et al., 2015</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ludwigsson et al., 2015</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>van der Maas et al., 2015</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Beau et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cleary et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Huang et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ma et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trotta et al., 2014</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Haberg et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ludwigsson et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rubenstein et al., 2013</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Fell et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hekkinen et al., 2012</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Kaikon et al., 2012</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Launay et al., 2012</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Lin et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pasternak et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pasternak et al., 2012b</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sammon et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MacKerrie et al., 2011</td>
<td>X</td>
<td>+</td>
</tr>
</tbody>
</table>

**Judgement**
- High (5-5 stars)
- Serious concerns (4-0 stars)
- Low (0-19 stars)
- No information

Legend:
- D1: Representativeness of exposed/cases
- D2: Selection of non-exposed/controls
- D3: Ascertainment of exposure/Case definition adequate
- D4: Demonstration that outcome was not present prior to exposure/Control definition adequate
- D5: Comparability of cohorts/cases and controls
- D6: Assessment of outcome/Assessment of exposure
- D7: Follow-up long enough for outcome to occur/Same exposure ascertainment for cases and controls
- D8: Losses to follow-up/Non-response in exposure ascertainment
Figure 6. Study-level ROB assessment results for observational studies evaluating (1) a combination of seasonal (TIIV and/or QIIV) and 2009 pandemic vaccine (MIIV) or (2) other pandemic vaccines alone or (3) comparing 2009 pandemic vaccine to pre-pandemic seasonal influenza vaccine, including primary outcomes with lowest ROB and highest ROB.

<table>
<thead>
<tr>
<th>Study</th>
<th>Low ROB primary outcome</th>
<th>High ROB primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td>Getahun et al., 2019</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sukumaran et al., 2018</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Kharbanda et al., 2017</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Shakhb et al., 2016</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cantu et al., 2013</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Chambers et al., 2013</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>Conlin et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Louik et al., 2013</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Richards et al., 2013</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Yamada et al., 2012</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Deinard et al., 1981</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

D1: Representativeness of exposed/cases  
D2: Selection of non-exposed/controls  
D3: Ascertainment of exposure/Case definition adequate  
D4: Demonstration that outcome was not present prior to exposure/Control definition adequate  
D5: Comparability of cohorts/cases and controls  
D6: Assessment of outcome/Ascertainment of exposure  
D7: Follow-up long enough for outcome to occur/ Same exposure ascertainment for cases and controls  
D8: Losses to follow-up/Non-response in exposure ascertainment

Judgement:  
- High (5-6 stars)  
- Some concerns (4-6 stars)  
- Low (1-3 stars)  
? No information
7. **GRADE Evidence Profile Table**

<table>
<thead>
<tr>
<th>Seasonal influenza vaccine (TIIV, QIIV) compared to no vaccine in pregnant women</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants (studies) Follow-up</strong></td>
<td><strong>Certainty assessment</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth (&lt; 37 completed weeks)</td>
<td></td>
</tr>
<tr>
<td>152,476 (5 observational studies)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence is very uncertain about the effects of seasonal influenza vaccine during pregnancy on the occurrence of preterm birth < 37 completed weeks.

| Spontaneous abortion (< 20 gestational weeks) | | | | serious\(^c\) | serious\(^d\) | not serious | serious\(^e\) | none | Very low | 46,917 (5.0%) | 14,983 (1.4%) | HR 0.77 (0.31 to 1.98) | Moderate |
| 1,900 (2 observational studies) | | | | 50 per 1,000 | 11 fewer per 1,000 (from 34 fewer to 42 more) |

The evidence is very uncertain about the effect of seasonal influenza vaccine during pregnancy on spontaneous abortion < 20 gestational weeks.
## Seasonal influenza vaccine (TIIV, QIIV) compared to no vaccine in pregnant women

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants (studies) Follow-up</strong></td>
<td><strong>Study event rates (%)</strong></td>
</tr>
<tr>
<td></td>
<td>With No vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>not serious</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stillbirths (≥ 18–22 gestational weeks or ≥ 500 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,475 cases, 12,119 controls; 5,076 exposed, 52,932 unexposed (2 observational studies)</td>
</tr>
<tr>
<td>Regan et al., 2016, reported an adjusted HR = 0.49 (0.29-0.84) in 58,008 pregnancies 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., 2020, found an adjusted OR = 0.98 (0.82-1.18). These two studies could not be pooled due to extremely high heterogeneity ($I^2 = 82.95$).</td>
</tr>
</tbody>
</table>

The evidence is very uncertain about the effect of seasonal influenza vaccine during pregnancy the occurrence of stillbirth ≥ 18–22 gestational weeks or ≥ 500 g.

<table>
<thead>
<tr>
<th>Small for gestational age birth (&lt; 10th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>297,424 (11 observational studies)</td>
</tr>
<tr>
<td>10657/165077 (6.5%)</td>
</tr>
</tbody>
</table>

| | Low | Moderate | High |
| | 37 per 1,000 | 60 per 1,000 | 136 per 1,000 |
| | 0 fewer per 1,000 (from 2 fewer to 1 more) | 1 fewer per 1,000 (from 3 fewer to 2 more) | 1 fewer per 1,000 (from 7 fewer to 5 more) |

The evidence is very uncertain about the effect of seasonal influenza vaccine during pregnancy on the occurrence of small-for-gestational-age birth < 10th percentile for gestational age and sex of a valid reference control group.
### Seasonal influenza vaccine (TIIV, QIIV) compared to no vaccine in pregnant women

#### Certainty assessment

<table>
<thead>
<tr>
<th>Study event rates (%)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With No vaccine</td>
<td></td>
<td>Risk with no vaccine</td>
</tr>
<tr>
<td>With seasonal influenza vaccine</td>
<td></td>
<td>Risk difference with seasonal influenza vaccine</td>
</tr>
</tbody>
</table>

#### Summary of findings

<table>
<thead>
<tr>
<th>Study event rates (%)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With No vaccine</td>
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<td>Risk with no vaccine</td>
</tr>
<tr>
<td>With seasonal influenza vaccine</td>
<td></td>
<td>Risk difference with seasonal influenza vaccine</td>
</tr>
</tbody>
</table>

#### Congenital anomalies from birth to 6 months of age

- **2,866 cases**
  - 1,411 controls (1 observational study)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Overall certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>◀◯◯◯ Very low</td>
</tr>
</tbody>
</table>

  Single case-control study reporting adjusted findings from 2,866 cases and 1,411 controls, indicating no significant effect of TIIV on congenital anomalies up to 6 months of age (aOR = 1.01 (0.85-1.21)).

The evidence is very uncertain about the effects of seasonal influenza vaccine during pregnancy on the occurrence of congenital anomalies identified from birth up to six months of age.

#### Congenital anomalies from birth to discharge

- **1,207**
  - (1 observational study)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Overall certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>◀◯◯◯ Very low</td>
</tr>
</tbody>
</table>

  Single cohort study found an aRR = 0.33 (0.04-2.73), with 2 events in 141 vaccinated pregnancies and 21 events in 1066 unvaccinated pregnancies.

The evidence is very uncertain about the effects of seasonal influenza vaccine during pregnancy on the occurrence of congenital anomalies identified from birth to discharge.

#### Maternal serious non-obstetrical adverse events: events unrelated to pregnancy causing hospitalization

- **1,051**
  - (1 observational study)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Overall certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>none</td>
<td>◀◯◯◯ Very low</td>
</tr>
</tbody>
</table>

  Single study (Munoz et al., 2005) found no apparent difference in risk between TIIV vaccinated (2 in 225) and unvaccinated women (3 in 826).

The evidence is very uncertain regarding the effect of seasonal influenza vaccination during pregnancy on hospitalization events within 42 days of vaccination.

#### Maternal serious non-obstetrical adverse events: not defined and time of follow-up not reported

- **346**
  - (1 observational study)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Overall certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>none</td>
<td>◀◯◯◯ Very low</td>
</tr>
</tbody>
</table>

  No events found in a single study (Singh et al., 2019) of 288 TIIV vaccinated and 58 unvaccinated women.

The evidence is very uncertain regarding the effect of seasonal influenza vaccination during pregnancy on non-obstetric SAEs, generally, for an undetermined time after vaccination.
**Seasonal influenza vaccine (TIIV, QIIV) compared to no vaccine in pregnant women**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Study event rates (%)</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With No vaccine</td>
<td>With seasonal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>influenza vaccine</td>
</tr>
<tr>
<td>Maternal serious non-obstetrical adverse events: inpatient Guillain-Barré syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study event rates (%)</td>
<td>With No vaccine</td>
<td>With seasonal influenza vaccine</td>
</tr>
<tr>
<td>223,898 (1 observational study)</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

The evidence is very uncertain about the effect of seasonal influenza vaccination during pregnancy on the occurrence of Guillain-Barré syndrome within 42 days of vaccination.

**Explanations**

a. 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 exposure in one study and assessment of the outcome in two studies.

b. The 95% CIs of the most heavily weighted study do not encompass the effect estimates of the three moderately weighted studies.

c. There were concerns regarding selection bias in both of the included studies.

d. Initial post-pandemic study found significantly increased risk, whereas no other study found significant effects.

e. The total sample size met the criteria for optimal information size, but the total number of events did not.

f. Neither of the CIs of the two studies contains the other’s effect estimate.

g. 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.

h. Serious ROB due to inadequate case definition (lack of description of the detection and reporting process of the surveillance system, its rigor, and whether active or passive), the unclear representativeness of the cases, and unclear non-response rate.

i. Concerns regarding biases related to selection and outcome assessment.

j. Total sample size is much lower than the optimal information size for the control group risk.

k. 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?”

l. Although country/countries of conduct was/were low-to-middle-income, the outcome shouldn’t be substantially different in the Canadian context.

m. The 95% CI of the single point estimate was extremely wide, encompassing potentially large harmful and beneficial effects.
8. Findings for monovalent 2009 pandemic H1N1 influenza vaccine vs no vaccine

Availability of the literature
Twenty-two cohort studies and two case-control studies reported data on the safety of monovalent 2009 pandemic H1N1 influenza vaccination during pregnancy and have been summarized in Supplement Tables 2 and 3 below, respectively. Studies that reported analyses that controlled for confounding in some manner (e.g., through matching, stratification, or statistical methods during analysis) were prioritized for synthesis for each outcome. We did not assess the GRADE certainty of evidence for any outcomes because only seasonal influenza vaccines were prioritized. Two retrospective cohort studies were conducted on overlapping data in Sweden and where these studies reported the same outcomes, to avoid double counting of participants, we elected to include in meta-analyses the study with the higher quality data (fewer missing data) and lower risk of bias (higher NOS score).

Preterm birth
Prioritized outcome

Four cohort studies reported the effects of 2009 pandemic vaccine compared to no vaccine or no 2009 H1N1-containing vaccine on preterm birth of less than 37 completed gestational weeks, using adjusted analyses that accounted for time at risk, minimizing immortal time bias. The findings from these studies were pooled in a meta-analysis and no significant effect of 2009 pandemic vaccine was found on preterm birth (aHR = 0.98, 95% CI = 0.90–1.07; I² = 45.358; Figure 7). Moderate statistical heterogeneity was present, potentially due to differences in inclusion criteria for infants (only singleton or live births) or presence of vaccine adjuvant. All studies had an apparent low likelihood of bias (NOS score 7 or 8 out of 9), with concerns regarding incomplete adjustment for all critical confounders in all studies and a high proportion of potential subjects with missing data in one study. Pooled findings for seven studies that reported adjusted analyses but did not account for time at risk have been provided in Figure 7 but should be interpreted with caution, given the impact of immortal time bias.

One of the studies that accounted for time at risk also reported a secondary analysis stratified by timing of vaccination and found a significant protective effect of vaccination during the first trimester (aHR = 0.88, 95% CI = 0.79–0.98), with the effect waning toward the null with each subsequent trimester of vaccination (second trimester: aHR = 0.90, 95% CI = 0.80–1.01; third trimester: aHR = 1.00, 95% CI = 0.85–1.20). This study also conducted a sensitivity analysis that accounted for duration of circulating H1N1 virus during a woman’s pregnancy using a time-varying covariate and found the results to be unaffected, indicating that any vaccine effect was unrelated to timing of conception relative to the influenza pandemic.

One other study reported an adjusted analysis and accounted for time at risk but was not included in the above meta-analysis because it compared 2009 pandemic vaccine to seasonal TIV given in the year prior to the pandemic. No significant effect of pandemic H1N1 MIV was found (aHR = 0.98, 95% CI = 0.85–
1.11). This study had a moderate risk of bias (NOS score 6 out of 9) due to concerns regarding selection of the unexposed cohort from a time period before the pandemic, as well as concerns regarding ascertainment of exposure data and incomplete adjustment of critical confounders.
Figure 7. Meta-analysis of observational studies reporting preterm birth at 37 completed weeks or less, comparing 2009 H1N1 monovalent influenza vaccine given at any time during pregnancy to no H1N1 vaccine and stratified by whether time at risk was accounted for (adjusted analyses only)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Adjuvanted?</th>
<th>Vax</th>
<th>No vax</th>
<th>Hazard ratio 95% CI</th>
<th>Relative weight</th>
<th>Singletons only</th>
<th>Livebirths only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vázquez-Benítez et al., 2016</td>
<td>US</td>
<td>No</td>
<td>7.01</td>
<td>0.91</td>
<td>1.00 1169 / 19157</td>
<td>2219 / 27392</td>
<td>35.84</td>
<td>Yes</td>
</tr>
<tr>
<td>Beau et al., 2014</td>
<td>France</td>
<td>No</td>
<td>8.03</td>
<td>0.97</td>
<td>1.24 NR / NR</td>
<td>NR / NR</td>
<td>8.08</td>
<td>Yes</td>
</tr>
<tr>
<td>Håberg et al., 2013</td>
<td>Norway</td>
<td>Yes</td>
<td>8.10</td>
<td>0.92</td>
<td>1.08 NR / 25976</td>
<td>NR / 87335</td>
<td>40.20</td>
<td>Yes</td>
</tr>
<tr>
<td>Fabiani et al., 2015</td>
<td>Italy</td>
<td>Yes</td>
<td>8.15</td>
<td>1.05</td>
<td>1.39 110 / 2000</td>
<td>5331 / 98229</td>
<td>15.89</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Adjuvanted?</th>
<th>Vax</th>
<th>No vax</th>
<th>Hazard ratio 95% CI</th>
<th>Relative weight</th>
<th>Singletons only</th>
<th>Livebirths only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary et al., 2014</td>
<td>Ireland</td>
<td>Both</td>
<td>8.07</td>
<td>0.56</td>
<td>0.89 141 / 3000</td>
<td>252 / 3877</td>
<td>8.46</td>
<td>Yes</td>
</tr>
<tr>
<td>Rubinstein et al., 2013</td>
<td>Argentina</td>
<td>Yes</td>
<td>7.79</td>
<td>0.69</td>
<td>0.90 354 / 7293</td>
<td>1505 / 23195</td>
<td>15.00</td>
<td>No</td>
</tr>
<tr>
<td>Huang et al., 2014</td>
<td>Taiwan</td>
<td>Both</td>
<td>7.90</td>
<td>0.83</td>
<td>0.97 806 / 9635</td>
<td>5392 / 9756</td>
<td>21.97</td>
<td>Yes</td>
</tr>
<tr>
<td>Fell et al., 2012</td>
<td>Canada</td>
<td>Both</td>
<td>8.95</td>
<td>0.86</td>
<td>1.02 1376 / 23280</td>
<td>2006 / 32091</td>
<td>22.54</td>
<td>Yes</td>
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<tr>
<td>van der Maas et al., 2015</td>
<td>Netherlands</td>
<td>Yes</td>
<td>6.98</td>
<td>0.59</td>
<td>1.62 54 / 1104</td>
<td>21 / 523</td>
<td>2.00</td>
<td>Yes</td>
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<tr>
<td>Ludvigsson et al., 2013</td>
<td>Sweden</td>
<td>Yes</td>
<td>9.99</td>
<td>0.89</td>
<td>1.10 635 / 13297</td>
<td>456 / 7790</td>
<td>18.21</td>
<td>Yes</td>
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<tr>
<td>Pedersen et al., 2012</td>
<td>Denmark</td>
<td>Yes</td>
<td>8.10</td>
<td>1.00</td>
<td>1.18 302 / 6543</td>
<td>295 / 6366</td>
<td>11.82</td>
<td>Yes</td>
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</table>

CI = confidence interval; MIV = monovalent influenza vaccine; NR = not reported; ROB = risk of bias; vax = vaccine
Numbers followed by plus signs (+) are lower than the total number included in the meta-analysis due to unreported raw data.
Spontaneous abortion and all-cause pregnancy loss
Many studies did not report spontaneous abortion specifically, but instead amalgamated all fetal deaths during pregnancy (i.e., all-cause pregnancy loss = spontaneous abortions and stillbirths) \(^{67} 69 74 78 81 91\). As well, many studies reported only raw data, with no analysis\(^{71} 79 81 82 86\), or unadjusted analyses\(^{85}\).

**Spontaneous abortion**

Ultimately, only one study reported adjusted analysis findings for SAB specifically, with follow-up time consistent with our standard definition (< 22 weeks of gestation) \(^{84}\). In that study, vaccination at any time during pregnancy with adjuvanted 2009 pandemic vaccine had no significant effect on spontaneous abortion. The study was large (n = 2,736 exposed; n = 32,672 unexposed), conducted in Denmark, and had a low risk of bias for an observational study.

**All-cause pregnancy loss**

Five studies reported the results of adjusted analyses assessing the impact of 2009 pandemic vaccine administered at any time during pregnancy compared to no vaccine on all-cause pregnancy loss \(^{67} 69 74 78 84\). When pooled, a protective effect of was found, with no statistical heterogeneity (aRR = 0.78, 95% CI = 0.68–0.90; \(I^2 = 0.00\); Figure 3). When only studies evaluating adjuvanted 2009 pandemic vaccine were pooled (n = 3) \(^{67} 74 84\), less of a protective effect was found (aRR = 0.84, 95% CI = 0.71–0.99; \(I^2 = 0.000\)). A sixth study (Conlin et al., 2013\(^{92}\)) compared a cohort of women in 2009 who received the 2009 H1N1 MIV with women who were pregnant the previous year and who received seasonal TiIV (2008–9), but was not included in the meta-analysis due to its non-standard comparator and resulting clinical heterogeneity.

The findings from all studies that reported either adjusted and unadjusted results for spontaneous abortion, specifically, or fetal death, generally, are illustrated below in Figure 4.

**Figure 3. Meta-analysis of cohort studies reporting all-cause pregnancy loss, comparing 2009 pandemic vaccine to no 2009 pandemic vaccine**

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjuvanted?</th>
<th>ROB</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>MV 2009</th>
<th>No vax</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludvigsson et al., 2015</td>
<td>Yes</td>
<td>8</td>
<td>0.83</td>
<td>0.66</td>
<td>1.05</td>
<td>115 / 1183</td>
<td>NR / 80796</td>
<td>0.78</td>
<td>37.06</td>
</tr>
<tr>
<td>Heberg et al., 2013</td>
<td>Yes</td>
<td>8</td>
<td>0.86</td>
<td>0.69</td>
<td>1.17</td>
<td>78 / 21976</td>
<td>414 / 87335</td>
<td>0.78</td>
<td>24.98</td>
</tr>
<tr>
<td>Pasternak et al., 2012</td>
<td>Yes</td>
<td>8</td>
<td>0.79</td>
<td>0.53</td>
<td>1.17</td>
<td>27 / 7682</td>
<td>1785 / 47523</td>
<td>0.78</td>
<td>13.34</td>
</tr>
<tr>
<td>Fall et al., 2012</td>
<td>Yes + No</td>
<td>8</td>
<td>0.66</td>
<td>0.47</td>
<td>0.92</td>
<td>60 / 23340</td>
<td>139 / 32330</td>
<td>0.78</td>
<td>18.75</td>
</tr>
<tr>
<td>Beau et al., 2014</td>
<td>No</td>
<td>8</td>
<td>0.56</td>
<td>0.31</td>
<td>1.01</td>
<td>13 / 1645</td>
<td>159 / 3290</td>
<td>0.78</td>
<td>5.87</td>
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</tbody>
</table>

CI = confidence interval; MIV = monovalent influenza vaccine; NR = not reported; ROB = risk of bias; vax = vaccine
Numbers followed by plus signs (+) are lower than the total number included in the meta-analysis due to unreported raw data.
Figure 4. Effects reported in cohort studies reporting spontaneous abortion or all-cause pregnancy loss, comparing 2009 pandemic vaccine to no 2009 pandemic vaccine or to no vaccine and stratified by adjusted analyses (top) and unadjusted analyses/raw data (bottom)

<table>
<thead>
<tr>
<th>Adjusted</th>
<th>Follow-up</th>
<th>Study</th>
<th>Adjusted?</th>
<th>Time of exposure</th>
<th>ROB</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Events / Total</th>
<th>Outcome definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>7-22 weeks</td>
<td>Painterman et al., 2012</td>
<td>Yes</td>
<td>Any time</td>
<td>8</td>
<td>1.11</td>
<td>0.71</td>
<td>1.73</td>
<td>20 / 2739</td>
<td>1699 / 32672</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lauzier et al., 2015</td>
<td>Yes</td>
<td>Any time</td>
<td>8</td>
<td>0.83</td>
<td>0.66</td>
<td>1.03</td>
<td>115 / 41153</td>
<td>859 / 82796</td>
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<tr>
<td></td>
<td>Isolation</td>
<td>Painterman et al., 2015</td>
<td>Yes</td>
<td>First trimester</td>
<td>8</td>
<td>0.97</td>
<td>0.71</td>
<td>1.32</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td></td>
<td>Isolation</td>
<td>Painterman et al., 2015</td>
<td>Yes</td>
<td>Second trimester</td>
<td>8</td>
<td>0.47</td>
<td>0.47</td>
<td>0.98</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td></td>
<td>Isolation</td>
<td>Painterman et al., 2015</td>
<td>Yes</td>
<td>Third trimester</td>
<td>8</td>
<td>0.82</td>
<td>0.52</td>
<td>1.30</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
<tr>
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<td>Isolation</td>
<td>Halling et al., 2013</td>
<td>Yes</td>
<td>NR</td>
<td>8</td>
<td>0.88</td>
<td>0.66</td>
<td>1.17</td>
<td>78 / 25878</td>
<td>414 / 87335</td>
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<tr>
<td></td>
<td>Isolation</td>
<td>Painterman et al., 2012</td>
<td>Yes</td>
<td>First trimester</td>
<td>8</td>
<td>0.96</td>
<td>0.63</td>
<td>1.47</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td></td>
<td>Isolation</td>
<td>Painterman et al., 2012</td>
<td>Yes</td>
<td>Second trimester</td>
<td>8</td>
<td>0.49</td>
<td>0.26</td>
<td>0.93</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
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<td>Painterman et al., 2012</td>
<td>Yes</td>
<td>Third trimester</td>
<td>8</td>
<td>0.23</td>
<td>0.31</td>
<td>1.69</td>
<td>NR / NR</td>
<td>NR / NR</td>
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<td>Isolation</td>
<td>Painterman et al., 2012</td>
<td>Yes</td>
<td>Any time</td>
<td>8</td>
<td>0.79</td>
<td>0.53</td>
<td>1.27</td>
<td>27 / 7062</td>
<td>1765 / 47523</td>
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<td>Isolation</td>
<td>Friell et al., 2012</td>
<td>No</td>
<td>NR</td>
<td>8</td>
<td>0.86</td>
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<td>1.60</td>
<td>60 / 23340</td>
<td>109 / 32200</td>
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<td>Beaz et al., 2014</td>
<td>No</td>
<td>NR</td>
<td>8</td>
<td>0.56</td>
<td>0.31</td>
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<td>131 / 16545</td>
<td>109 / 3290</td>
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<td>Conlin et al., 2013</td>
<td>No</td>
<td>NR</td>
<td>8</td>
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<td>0.78</td>
<td>1.29</td>
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<td>Lin et al., 2012</td>
<td>Yes</td>
<td>NR</td>
<td>8</td>
<td>NE</td>
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<td>0 / 198</td>
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<td>No</td>
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<td>Heijlaken et al., 2012</td>
<td>Yes</td>
<td>NR</td>
<td>4</td>
<td>0.05</td>
<td>0.00</td>
<td>0.87</td>
<td>0 / 2295</td>
<td>9 / 2213</td>
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<tr>
<td></td>
<td>9-12 weeks</td>
<td>Summon et al., 2012</td>
<td>Yes</td>
<td>Any time</td>
<td>7</td>
<td>0.74</td>
<td>0.62</td>
<td>0.88</td>
<td>NR / NR</td>
<td>NR / NR</td>
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<td>9-12 weeks</td>
<td>Sammon et al., 2012</td>
<td>Yes</td>
<td>Within 28 days</td>
<td>7</td>
<td>0.56</td>
<td>0.43</td>
<td>0.73</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td></td>
<td>13-24 weeks</td>
<td>Sammon et al., 2012</td>
<td>Yes</td>
<td>Any time</td>
<td>8</td>
<td>0.59</td>
<td>0.45</td>
<td>0.77</td>
<td>NR / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td></td>
<td>13-24 weeks</td>
<td>Sammon et al., 2012</td>
<td>Yes</td>
<td>Within 28 days</td>
<td>8</td>
<td>0.45</td>
<td>0.28</td>
<td>0.73</td>
<td>NR / NR</td>
<td>NR / NR</td>
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<tr>
<td></td>
<td>Isolation</td>
<td>Lauzier et al., 2012</td>
<td>No</td>
<td>NR</td>
<td>5</td>
<td>0.56</td>
<td>0.06</td>
<td>5.50</td>
<td>1 / 320</td>
<td>3 / 557</td>
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<tr>
<td></td>
<td>Isolation</td>
<td>Mau et al., 2014</td>
<td>Yes</td>
<td>NR</td>
<td>5</td>
<td>0.43</td>
<td>0.43</td>
<td>0.83</td>
<td>1 / 122</td>
<td>2 / 104</td>
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<td></td>
<td>Isolation</td>
<td>Mau et al., 2014</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
<td>0.74</td>
<td>0.04</td>
<td>14.51</td>
<td>2 / 80</td>
<td>0 / 11</td>
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<tr>
<td></td>
<td>Isolation</td>
<td>Mackenzie et al., 2011</td>
<td>Yes</td>
<td>First trimester</td>
<td>5</td>
<td>3.72</td>
<td>0.20</td>
<td>71.12</td>
<td>2 / 15</td>
<td>0 / 11</td>
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<td></td>
<td>Isolation</td>
<td>Mackenzie et al., 2011</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>0 / 43</td>
<td>0 / 11</td>
</tr>
<tr>
<td></td>
<td>Isolation</td>
<td>Mackenzie et al., 2011</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>0 / 22</td>
<td>0 / 11</td>
</tr>
</tbody>
</table>

MIV = monovalent influenza vaccine; NR = not reported; ROB = risk of bias; TIIV = trivalent inactivated influenza vaccine; vax = vaccine

Conlin et al., 2013 compared women receiving non-adjuvanted 2009 pandemic H1N1 influenza vaccine to women who were pregnant the previous year and who received seasonal TIIV.
Stillbirth

Eleven cohort studies and one case-control study assessed the effects of 2009 pandemic vaccine on stillbirths. Seven of these studies reported adjusted analyses and their findings have been pooled, after stratifying by whether temporal biases were accounted for. When temporal biases were accounted for, a non-significant trend toward a protective effect was found (aHR = 0.85, 95% CI = 0.45–1.61; $I^2 = 54.25$; Figure 5). When temporal biases were not accounted for, the protective effect was significant (aRR = 0.75, 95% CI = 0.60–0.92; $I^2 = 5.80$; Figure 5).

Many studies reported exposure only during the second or third trimester, reflecting restrictions on vaccination of women with the novel pandemic vaccine during the first trimester in many countries. Where data in a study were reported by trimester and overall, we have included the overall data in the meta-analysis. One case-control study reported a significant protective effect of vaccination during the second or third trimester but not during the first trimester; however, differences in significance in the three trimesters of vaccination were not found in a cohort study. Another cohort study evaluated the potential impact of prevention of infection and the potential impact of vaccine toxicity on stillbirth by using differing time periods at risk: stillbirths occurring during any week subsequent to vaccination (infection prevention) and stillbirths occurring within 28 days of vaccination (toxicity). No significant findings were identified for either model, although only unadjusted analysis results were reported (infection prevention model: HR = 0.70, 95% CI = 0.47–1.03; toxicity model: HR = 1.56, 95% CI = 0.73–3.34).

All studies were conducted in upper middle- to high-income countries, and outcome definitions generally agreed with the prioritized standard definition, except for two studies, one reporting adjusted results and the other unadjusted results. Three studies did not report an outcome definition. No trends were obvious as the cut-off between spontaneous abortions and stillbirths increased (Figure 5). The majority of studies were conducted in European countries where only adjuvanted 2009 pandemic vaccines were available; however, four studies reported data for non-adjuvanted vaccine or a combination of adjuvanted and non-adjuvanted vaccines. Again, there were no obvious differences in findings in studies that evaluated adjuvanted, non-adjuvanted, or a combination of vaccines (Figure 5).
**Figure 5. Meta-analyses of observational studies reporting stillbirth as an outcome, comparing 2009 pandemic vaccine to no 2009 pandemic vaccine, sorted by follow-up time and stratified by whether immortal time bias was accounted for**

<table>
<thead>
<tr>
<th>Accounted For ITB?</th>
<th>Outcome definition</th>
<th>Study name</th>
<th>Adjuvanted?</th>
<th>Time of exposure</th>
<th>ROB</th>
<th>Risk ratio</th>
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<td>0.57</td>
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<td>533 / 138931</td>
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<td></td>
<td></td>
<td></td>
<td>0.75 / 0.60</td>
<td>0.92 / 0.60</td>
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**ITB = immortal time bias; MIV = monovalent inactivated influenza vaccine; ROB = risk of bias**
Small-for-gestational-age birth

Eight cohort and two case-control studies reported findings for small-for-gestational-age birth (< 10th percentile on any scale), evaluating 2009 pandemic vaccine. Eight of these reported adjusted analysis results and were pooled in a meta-analysis (Figure, Panel A). Vaccination occurred at any time during pregnancy in some studies, but was limited to only the second or third trimester in others due to recommendations against first trimester vaccination. Where analyses were reported that were stratified by trimester of exposure, we included data for the overall pregnancy. The studies in the forest plot have been sorted by use of adjuvanted vaccine. A significant protective effect of pandemic 2009 H1N1 vaccination was identified against SGA births (aRR = 0.95, 95% CI = 0.91–0.99; I² = 36.10). When only studies reporting findings for any trimester exposure were pooled, the same approach as was used in our meta-analyses of TIIV studies, there was no association between vaccination and SGA (aRR = 1.00, 95% CI = 0.93–1.07; I² = 31.54; Figure 11, Panel B, lowest plot).

When the meta-analysis was stratified by trimester of exposure, the only significant protective effect found was for women vaccinated in the second or third trimester (aRR = 0.92, 95% CI = 0.89–0.95; Figure, Panel B). A trend was apparent as exposure moved from first to second to third trimester, relative risks increased and moved from favouring vaccine to favouring no vaccine; however, none of these effects were significant (first trimester: aRR = 0.87, 95% CI = 0.75–1.02; second trimester: aRR = 0.99, 95% CI = 0.83–1.19; third trimester: aRR = 1.08, 95% CI = 0.98–1.20). This trend is counter to the protective effect found in the stratum for exposure during the second or third trimester. High statistical heterogeneity was present in the first and second trimester strata (I² = 74.33 and 76.837, respectively), moderate in the “any trimester” stratum (I² = 31.54), and no heterogeneity was apparent in the other strata (I² = 0.000).
Figure 11. Meta-analysis of observational studies reporting small-for-gestational-age birth, < 10th percentile on any scale, comparing 2009 pandemic vaccine to no vaccine (adjusted analyses only). Panel A: exposure during any gestational week or during second or third trimester. Panel B: stratified by timing of exposure.

### Panel A

<table>
<thead>
<tr>
<th>Study name</th>
<th>Country</th>
<th>Adjusted?</th>
<th>ROB</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Vax</th>
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<th>Events / Total</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight</th>
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<tr>
<td>Vazquez-Benitez et al., 2016</td>
<td>US</td>
<td>No</td>
<td>7</td>
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<td>0.99</td>
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<td>1922</td>
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<td>Ricardos et al., 2013</td>
<td>US</td>
<td>No</td>
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<td>99</td>
<td>1006</td>
<td>123 / 1505</td>
<td>162 / 183</td>
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<td>1123</td>
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<td>Italy</td>
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<td>0.84</td>
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<td>5793</td>
<td>2134 / 22165</td>
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<th>Upper Limit</th>
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<td>Richards et al., 2013</td>
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<td>1094</td>
<td>123 / 1905</td>
<td>5.51</td>
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CI = confidence interval; MIV = monovalent inactivated influenza vaccine; ROB = risk of bias; vax = vaccine

### Congenital anomalies

Nine cohort studies evaluating 2009 pandemic vaccine\textsuperscript{65} and one case-control study\textsuperscript{100} reported findings regarding congenital anomalies; however, only five of these studies reported adjusted
results and only two reported findings specifically for women vaccinated in the first trimester. A meta-analysis was conducted, stratified by timing of vaccination, with first trimester exposure as the primary stratum and all other timings of vaccination pooled into the other stratum (Figure 12). Two studies reported adjusted findings for first trimester exposure to adjuvanted vaccine and when pooled, no effect of first-trimester vaccination was found (aRR = 1.00, 95% CI = 0.83–1.22; I^2 = 0.00; Figure 12). One study accounted for 98.19% of the effect. Both adjuvanted and non-adjuvanted vaccine had been used in one study, with results stratified by vaccine type. To reduce heterogeneity, we included only adjuvanted vaccine findings from this study in the primary meta-analysis. When both adjuvanted and non-adjuvanted vaccine data were included, there was high statistical heterogeneity (I^2 = 74.251) and there was marked imprecision of the estimate, demonstrated by an extremely wide confidence interval (aRR = 0.74, 95% CI = 0.35–1.58).

Four studies reported findings for women vaccinated at any time during pregnancy or during the second or third trimesters. The time allowed for identification of congenital anomalies varied in the studies from at birth, to the time to discharge, to up to 7 days, 3 months, and 6 months of age. One study reported findings for data collected at birth and up to 6 months of age. Initially for this study, we included findings for data collected up to 6 months of age in the meta-analysis (Figure 12). No study reported a significant effect, and when pooled, the effect of vaccination at any time during pregnancy remained non-significant (aRR = 1.11, 95% CI = 0.98–1.26; I^2 = 42.51; Figure 12). Moderate heterogeneity was present, mainly due to the study that identified anomalies up to 6 months of age. When we replaced the 6-month findings with the at-birth findings, statistical heterogeneity was reduced to zero and the effect estimate demonstrated a significant negative impact of pandemic vaccination at any time during pregnancy on congenital anomalies (aRR = 1.15, 95% CI = 1.02–1.31). One study influenced the estimate substantially, with a weight of 82.49% of the effect.

Amongst studies reporting unadjusted results or raw data, no significant effects were reported (Figure 12).
Figure 12. Meta-analysis of observational studies reporting congenital anomalies, comparing 2009 pandemic vaccine to no vaccine (adjusted analyses only; Panel A) and findings from studies reporting unadjusted results or raw data (Panel B).

Panel A

<table>
<thead>
<tr>
<th>First trimester?</th>
<th>Study</th>
<th>Country</th>
<th>Adjuvanted?</th>
<th>ROB</th>
<th>Timing of exposure</th>
<th>Timing of measurement</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Anomalies / Total</th>
<th>No 2009 MV</th>
<th>MIV 2009 MV</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight</th>
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<td>7 days</td>
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<td>NR / NR</td>
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<td>NR / NR</td>
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<td>NR</td>
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CI = confidence interval; MIV = monovalent inactivated influenza vaccine; NR = not reported; NE = not estimable; ROB = risk of bias
Numbers followed by plus signs (+) are lower than the total number included in the meta-analysis due to unreported raw data.

Panel B

<table>
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<th>First trimester?</th>
<th>Study</th>
<th>Country</th>
<th>Adjuvanted?</th>
<th>ROB</th>
<th>Timing of exposure</th>
<th>Timing of measurement</th>
<th>Risk ratio</th>
<th>Lower limit</th>
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<th>Anomalies / Total</th>
<th>No 2009 MV</th>
<th>MIV 2009 MV</th>
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<td>110 / 3898</td>
<td>25 / 252</td>
<td>36 / 200</td>
<td></td>
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<td></td>
<td>Rubinstein et al., 2013</td>
<td>Argentina</td>
<td>Yes</td>
<td>4</td>
<td>Any trimester</td>
<td>7 days</td>
<td>0.81</td>
<td>0.56</td>
<td>1.38</td>
<td>35 / 2593</td>
<td>110 / 3895</td>
<td>25 / 252</td>
<td>36 / 200</td>
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<tr>
<td></td>
<td>Mackenzie et al., 2011</td>
<td>Scotland</td>
<td>Both</td>
<td>3</td>
<td>Any trimester</td>
<td>at birth</td>
<td>1.67</td>
<td>0.10</td>
<td>28.33</td>
<td>5 / 78</td>
<td>0 / 11</td>
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<td></td>
<td>Leyvay et al., 2012</td>
<td>France</td>
<td>No</td>
<td>4</td>
<td>Second or third trimester</td>
<td>at birth</td>
<td>2.32</td>
<td>0.52</td>
<td>10.30</td>
<td>4 / 120</td>
<td>3 / 507</td>
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<td></td>
<td>Mackenzie et al., 2011</td>
<td>Scotland</td>
<td>Both</td>
<td>3</td>
<td>Second trimester</td>
<td>at birth</td>
<td>2.45</td>
<td>0.14</td>
<td>42.48</td>
<td>4 / 120</td>
<td>0 / 11</td>
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<tr>
<td></td>
<td>Mackenzie et al., 2011</td>
<td>Scotland</td>
<td>Both</td>
<td>3</td>
<td>Third trimester</td>
<td>at birth</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>0 / 22</td>
<td>0 / 11</td>
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</table>

CI = confidence interval; MIV = monovalent inactivated influenza vaccine; NR = not reported; NE = not estimable; ROB = risk of bias
Numbers followed by plus signs (+) are lower than the total number included in the meta-analysis due to unreported raw data.

Maternal serious non-obstetric events
No studies of any design reported maternal non-obstetric SAEs for 2009 pandemic vaccine.

Low birth weight
Eight observational studies evaluating 2009 pandemic vaccines reported adjusted analyses for low birth weight measured as < 2,500 g at any gestational age at birth and any birth status (alive or stillborn) and were pooled in a meta-analysis. The studies were stratified by gestational age at birth, with six studies including infants born at gestational ages at full term and under 65 75 77 79 83 100 and two studies including only full-term infants. 66 74. All studies evaluated adjuvanted pandemic vaccines, although one study included both adjuvanted and non-adjuvanted vaccines (9.3% and 90.7 of exposed women, respectively).
All but one of the studies demonstrated a relatively low risk of bias (7–9 NOS score), with the final study receiving a score of 6. In the studies including any gestational age infant, adjusted odds and hazard ratios ranged from 0.74 to 1.14, with two studies demonstrating significant protective effects and all other studies’ confidence intervals overlapping the null line. (Note that odds and hazard ratios have been reported as risk ratios in the forest plot.) When the seven studies were pooled, no significant effect of vaccination on low birth weight was found (aRR = 0.89, 95% CI = 0.78–1.02; I² = 75.26; Figure 14). There was substantial statistical heterogeneity amongst the six studies (I² = 75.26), which decreased slightly when each of the Scandinavian studies was removed, independently, and decreased to zero when all three Scandinavian studies were removed. These three studies had the highest effect sizes (i.e., all close to null) and all were statistically not significant. The other four studies reported effects that were protective of low birth weight, two of which were statistically significant. Other than locations of the studies (Scandinavia or not), no obvious differences in definitions, timings of exposure, or methods of analysis were apparent that could account for the statistical heterogeneity.

Hazard ratios reported in the two studies that included only full-term infants ranged from 0.90 to 0.92 and were non-significant. Similar to the stratum of any gestational age infants, a non-significant protective effect was found with meta-analysis (aRR = 0.91, 95% CI = 0.78–1.05, I² = 0.00; Figure 14). No statistical heterogeneity was evident.

When all nine studies were pooled, an overall significant protective effect of pandemic vaccination was found against low birth weight (aRR = 0.89, 95% CI = 0.81–0.98; I² = 67.52; Figure 14). Pooling of the strata augmented the total sample size and increased the power of the meta-analysis to detect a difference between vaccinated and unvaccinated women. There was substantial heterogeneity in the overall analysis (I² = 67.572), attributed mainly to the three Scandinavian studies in the first strata. When non-Scandinavian studies were retained for analysis, heterogeneity dropped to zero and overall effects were highly significant (aRR = 0.79, 95% CI = 0.74–0.85); however, when the four Scandinavian studies were pooled, moderate heterogeneity was present (I² = 42.633) and overall effects were clearly not statistically significant (aRR = 0.99, 95% CI = 0.89–1.10). Thus, Scandinavian studies were different in some way from studies from other areas of the world, and also moderately different amongst themselves.
### Supplement Table 2. Characteristics of 31 cohort studies that evaluated vaccines other than seasonal influenza vaccine, sorted by vaccine evaluated, included in the systematic review of the safety of influenza vaccination during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of conduct</th>
<th>Design</th>
<th>Funding</th>
<th>Objective</th>
<th>Recruitment period</th>
<th>Number of women (number of infants)</th>
<th>Interventions compared</th>
<th>Safety endpoints of interest</th>
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</thead>
<tbody>
<tr>
<td><strong>Studies comparing 2009 H1N1 pandemic vaccine to no vaccine (or no H1N1 vaccine) (n = 22)</strong></td>
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<tr>
<td>Ludvigsson et al., 2016&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>Non-industry</td>
<td>To examine the risk for any congenital malformation, and specifically congenital heart disease (CHD), oral cleft, and limb deficiency, in a large population-based cohort that included more than 40 000 offspring of mothers exposed to Pandemrix.</td>
<td>Births from 1 October 2009 to 1 October 2011</td>
<td>137,660 (97,869)</td>
<td>H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)</td>
<td>Specific congenital anomalies</td>
</tr>
<tr>
<td>Vazquez-Benitez et al., 2016&lt;sup&gt;6&lt;/sup&gt;</td>
<td>USA</td>
<td>Retrospective</td>
<td>Non-industry and Insurance</td>
<td>To discuss the potential biases in the associations of maternal MIV vaccination with preterm and small-for-gestational-age (SGA) births.</td>
<td>Births from 1 January 2009 to 31 December 2010</td>
<td>46,549 (46,549)</td>
<td>H1N1 monovalent inactivated No H1N1 monovalent (27% received seasonal TIIV)</td>
<td>PTB, SGA</td>
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<tr>
<td>Baum et al., 2015&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Finland</td>
<td>Retrospective</td>
<td>Non-industry</td>
<td>A population-wide register study on the safety of the AS03 adjuvanted pandemic influenza vaccine given during pregnancy. Due to lack of evidence in the literature, we specifically focus on the safety of vaccination during the first trimester of pregnancy.</td>
<td>Pregnant on 1 November 2009</td>
<td>43,604 (43,604)</td>
<td>H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)</td>
<td>Stillbirth, PTB, LBW, SGA</td>
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<tr>
<td>Study</td>
<td>Objective</td>
<td>Recruitment period</td>
<td>Number of women (number of infants)</td>
<td>Interventions compared</td>
<td>Safety endpoints of interest</td>
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<td>Fabiani et al., 2015</td>
<td>To evaluate the risk of adverse maternal, fetal and neonatal outcomes associated with the administration of the MF59-adjuvanted A/H1N1 pdm09 influenza vaccine among Italian pregnant women and their newborns.</td>
<td>Births from 15 October 2009 to 30 September 2010 with start dates from 15 January 2009 to 31 December 2009</td>
<td>100,332 (100,332)</td>
<td>H1N1 monovalent MF59-adjuvanted (Focetria, Novartis)</td>
<td>Stillbirth, PTB, LBW, congenital anomalies</td>
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<tr>
<td>Ludvigsson et al., 2015</td>
<td>To explore mortality in the offspring of mothers who received influenza A(H1N1)pdm09 vaccination and to examine stillbirth, early neonatal death, and offspring mortality after taking familial factors into account.</td>
<td>Births from 1 October 2009 to 31 December 2012</td>
<td>137,886 (121,979)</td>
<td>H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)</td>
<td>Fetal death</td>
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<td>van der Maas et al., 2015</td>
<td>To assess the possible impact of vaccination with Focetria during the second and third trimesters of pregnancy on pregnancy outcomes and growth, development and infection-related contacts with the general practitioner of the infants up to 1 year of age</td>
<td>Pregnant between November and December 2009</td>
<td>1,736 (1,736)</td>
<td>H1N1 monovalent MF59-adjuvanted (Focetria, Novartis)</td>
<td>Maternal death, PTB, SGA</td>
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<tr>
<td>Beau et al., 2014</td>
<td>To evaluate the potential adverse effects of A/H1N1 vaccination, mainly with a non-adjuvanted vaccine, during pregnancy in France.</td>
<td>Births from 21 October 2009 to 30 November 2010, with start dates before 31 January 2010</td>
<td>12,120 (4,762)</td>
<td>H1N1 monovalent unadjuvanted (over 93% of women) OR AS03-adjuvanted OR MF59-adjuvanted OR AF03-adjuvanted (Panenza (93% of women), Pandemrix, Celvapan, Focetria, Humenza)</td>
<td>Fetal death, PTB, SGA</td>
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<td>Study</td>
<td>Objective</td>
<td>Recruitment period</td>
<td>Number of women (number of infants)</td>
<td>Interventions compared</td>
<td>Safety endpoints of interest</td>
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| Cleary et al., 2014️️️️| To describe the uptake and determinants of 2009 A/H1N1 influenza vaccination in pregnant women during the pandemic and to determine if there is an association between vaccination and adverse pregnancy outcomes. | Births from 1 December 2009 to 30 September 2010 | 6,894 (6,894)                        | H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)  
H1N1 unadjuvanted (Celvapan)  
No H1N1 vaccine                                                                 | PTB, SGA, congenital anomalies                                                               |
| Ma et al., 2014️️️️️  | To monitor and evaluate the safety of pregnant women who have been inoculated with the influenza A(H1N1) vaccine; to study the impact of the vaccine on the fetus and newborn and to report the results. | During pregnancy: dates not reported | 226 (NA)                            | H1N1 monovalent unadjuvanted inactivated split-virion  
No vaccine                                                                 | SAB, PTB, LBW                                                                               |
| Trotta et al., 2014️️️️| To estimate the risk of adverse outcomes during pregnancy, in both mothers and newborns, in association with the pandemic vaccination | Births from 1 October 2009 to 30 September 2010 | 30,118 (11,269)                     | H1N1 monovalent MF59-adjuvanted (Focetria, Novartis)  
No vaccine                                                                 | Stillbirth, SGA, congenital anomalies, early neonatal death                                |
| Håberg et al., 2013️️️️| To assess the effectiveness of the pandemic vaccine in pregnant women in Norway and the effect of vaccination or influenza on fetal survival | Births in 2009 or 2010, with start dates earlier than 43 weeks before December 2010 | 113,331 (113,331)                   | H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)  
No H1N1 vaccine                                                                 | PTB, LBW                                                                                   |
| Ludvigsson et al., 2013️️️️| To examine the risks of adverse pregnancy outcomes in pregnant women undergoing H1N1 vaccination, by conceptualizing the observational cohort as a series of | Pregnancies conceived between February 2009 and January 2010 | 21,087 (21,087)                     | H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)  
No H1N1 vaccine                                                                 | PTB, LBW, SGA                                                                               |
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Recruitment period</th>
<th>Number of women (number of infants)</th>
<th>Interventions compared</th>
<th>Safety endpoints of interest</th>
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</thead>
<tbody>
<tr>
<td>Rubinstein et al., 2013&lt;sup&gt;27&lt;/sup&gt;</td>
<td>To compare the occurrence of perinatal outcomes in mothers and children between pregnant women vaccinated with monovalent MF59 adjuvanted influenza A/H1N1 and a non-vaccinated group; to evaluate the association between monovalent MF59 adjuvanted influenza A/H1N1 vaccine and risk of perinatal events in subgroups defined by exposure status and baseline risk of adverse events.</td>
<td>Births from September 2010 to May 2011</td>
<td>30,488 (30,729)</td>
<td>H1N1 monovalent MF59-adjuvanted inactivated (Focetria, Novartis)</td>
<td>Stillbirth, PTB, LBW, congenital anomalies</td>
</tr>
<tr>
<td>Fell et al., 2012&lt;sup&gt;28&lt;/sup&gt;</td>
<td>To examine the association between maternal H1N1 influenza vaccination and fetal and neonatal outcomes.</td>
<td>Births from 2 November 2009 to 30 April 2010</td>
<td>55,570 (55,570)</td>
<td>H1N1 monovalent inactivated with or without seasonal vaccination</td>
<td>Fetal death, PTB, SGA</td>
</tr>
<tr>
<td>Heikkinen et al., 2012&lt;sup&gt;29&lt;/sup&gt;</td>
<td>To assess the safety of the MF59-adjuvanted A/H1N1 influenza vaccine during the recent pandemic.</td>
<td>Pregnant or recently pregnant from January to August 2010 (the Netherlands), May to June 2010 (Italy), or July to August 2010 (Argentina)</td>
<td>4,508 (4,540)</td>
<td>H1N1 monovalent MF59-adjuvanted (Focetria, Novartis) No vaccine (seasonal vaccine unavailable)</td>
<td>SAB, stillbirth, PTB, LBW, congenital anomalies</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Recruitment period</td>
<td>Number of women (number of infants)</td>
<td>Interventions compared</td>
<td>Safety endpoints of interest</td>
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</table>
| Källén et al., 2012<sup>80</sup> Sweden  
Retrospective  
No funding | To describe neonatal outcomes after H1N1 vaccination: the presence of congenital malformations, preterm birth, low birthweight, and intrauterine growth restriction. | Births from 1 October 2009 to 31 December 2010 | 155,526 (157,775) | H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)  
No Pandemrix vaccine (included pandemic period and pre-pandemic group in which women could have been vaccinated with seasonal influenza vaccine) | Stillbirths, PTB, LBW, SGA, congenital anomalies |
| Launay et al., 2012<sup>81</sup> France  
Prospective  
Non-industry | To assess: 1) the incidence of laboratory-documented influenza 2009 pandemic, 2) the effects of pandemic vaccination on pregnancy outcome and 3) the proportion of women with seroprotection against influenza 2009 A/H1N1 at delivery, both in vaccinated and in nonvaccinated women | Pregnant during 12 October 2009 to 3 February 2010 | 877 (869) | H1N1 monovalent unadjuvanted (Panenza)  
No vaccine | Stillbirth, PTB, LBW, congenital anomalies |
| Lin et al., 2012<sup>82</sup> Taiwan  
Retrospective  
Industry | To observe the safety profile of the AdimFlu-S® influenza A (H1N1) vaccine in pregnant women to understand the risk posed by vaccines and anticipate questions that the public may have about their safety. | Pregnant during the influenza season between October 2009 and February 2010 | 396 (408) | H1N1 monovalent unadjuvanted inactivated split-virion (AdimFlu-S)  
No vaccine (no seasonal vaccine administered) | SAB, stillbirth, PTB, LBW, congenital anomalies |
| Pasternak et al., 2012<sup>83</sup> Denmark  
Retrospective  
Non-industry | To investigate whether exposure to an AS03-adjuvanted influenza A(H1N1) pdm09 vaccine in pregnancy was associated with increased risk of major birth defects, preterm birth, and fetal growth restriction | Births from 2 November 2009 to 30 September 2010, with start date after 1 February 2009 and before 31 December 2009 | 53,432 (53,432) | H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)  
No H1N1 vaccine | PTB, LBW, SGA |
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Recruitment period</th>
<th>Number of women (number of infants)</th>
<th>Interventions compared</th>
<th>Safety endpoints of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasternak et al., 2012&lt;sup&gt;84&lt;/sup&gt;</td>
<td>To investigate whether there was an increased risk of fetal death (spontaneous abortion and stillbirth) after vaccination with an AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine among pregnant women in Denmark.</td>
<td>Births from 2 November 2009 to 30 September 2010, with start date after 1 February 2009 and before 06 December 2009</td>
<td>54,585 (54,585)</td>
<td>H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)</td>
<td>SAB, fetal death, stillbirth</td>
</tr>
<tr>
<td>Denmark</td>
<td>Retrospective</td>
<td>Non-industry</td>
<td></td>
<td>No H1N1 vaccine</td>
<td></td>
</tr>
<tr>
<td>Sammon et al., 2012&lt;sup&gt;85&lt;/sup&gt;</td>
<td>To investigate whether the hazard of foetal death is altered in pregnancies vaccinated against influenza A(H1N1)pdm09</td>
<td>Births from 21 October 2009 to 1 January 2010</td>
<td>39,863 (NA)</td>
<td>H1N1 monovalent AS03-adjuvanted inactivated split-virion (Pandemrix)</td>
<td>SAB, stillbirth</td>
</tr>
<tr>
<td>UK</td>
<td>Retrospective</td>
<td>No funding</td>
<td></td>
<td>No vaccine</td>
<td></td>
</tr>
<tr>
<td>Mackenzie et al., 2011&lt;sup&gt;86&lt;/sup&gt;</td>
<td>(i) to recruit cohorts of people offered H1N1 influenza A vaccination: vaccinated and unvaccinated (unexposed) cohorts (those eligible for vaccination but who did not receive it), (ii) to examine the use and safety of H1N1 influenza A vaccination during the vaccination programme with particular interest in vaccine utilization characteristics for the whole vaccinated cohort and selected clinical risk groups (pregnant women, adults with selected underlying conditions, frontline health care workers), (iii) to capture patient self-reported events, (iv) to describe cases of serious adverse events (resulting in or prolonging hospital admission, life-threatening, fatal or resulting in congenital anomalies</td>
<td>Pregnant during 2 November 2009 to 30 April 2010</td>
<td>113 (117)</td>
<td>H1N1 monovalent</td>
<td>SAB, stillbirth, congenital anomalies</td>
</tr>
<tr>
<td>Scotland</td>
<td>Prospective</td>
<td>No funding</td>
<td></td>
<td>No H1N1 vaccine (over half received seasonal vaccine)</td>
<td></td>
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<tr>
<td>Study</td>
<td>Objective</td>
<td>Recruitment period</td>
<td>Number of women (number of infants)</td>
<td>Interventions compared</td>
<td>Safety endpoints of interest</td>
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<tr>
<td>Getahun et al., 2019&lt;sup&gt;87&lt;/sup&gt;</td>
<td>To examine the safety of seasonal influenza vaccination in pregnant women from a large, ethnically diverse, patient population and explore if the association is modified by race/ethnicity, timing and type of vaccination.</td>
<td>Pregnant during influenza seasons between 1 January 2008 and 31 December 2016</td>
<td>237,738 (237,738)</td>
<td>Seasonal pre- and post-pandemic (TIIV) and 2009 pandemic</td>
<td>Stillbirth, PTB, SGA</td>
</tr>
<tr>
<td>Kharbanda et al., 2017&lt;sup&gt;88&lt;/sup&gt;</td>
<td>To examine risks for major structural birth defects after maternal receipt of IIV in the first trimester</td>
<td>Births between 1 January 2004 and 1 September 2013</td>
<td>425,944 (425,944)</td>
<td>Seasonal pre- and post-pandemic (TIIV) and 2009 pandemic</td>
<td>Specific congenital anomalies</td>
</tr>
<tr>
<td>Shakib et al., 2016&lt;sup&gt;89&lt;/sup&gt;</td>
<td>To identify the proportion of delivering women reporting influenza vaccine in pregnancy and compare influenza outcomes in the first 6 months in infants born to</td>
<td>Pregnant between 1 December 2005 and 31 March 2014</td>
<td>245,386 (249,387)</td>
<td>Seasonal pre- and post-pandemic (TIIV and QIIV) and 2009 pandemic</td>
<td>PTB</td>
</tr>
</tbody>
</table>

Studies evaluating interventions that were not purely seasonal (TIIV and/or QIIV) or 2009 H1N1 pandemic vaccine, or that compared to an unexposed group other than “no vaccine” or “no H1N1 vaccine” (n = 9)
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Recruitment period</th>
<th>Number of women (number of infants)</th>
<th>Interventions compared</th>
<th>Safety endpoints of interest</th>
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</thead>
<tbody>
<tr>
<td>Cantu et al., 2013</td>
<td>To identify the characteristics of women who accept the flu vaccine and to screen the hypothesis that vaccination during pregnancy prevents adverse fetal outcomes.</td>
<td>Pregnant during 1 October to 31 December in 2009 or 2010</td>
<td>2,989 (2,989)</td>
<td>2009 pandemic with or without 2009–10 seasonal (TIIV)</td>
<td>SAB, stillbirth, PTB, SGA</td>
</tr>
<tr>
<td>Chambers et al., 2013</td>
<td>To evaluate the fetal risk and relative safety of the pH1N1 influenza vaccine using data from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), a research program developed specifically to evaluate medications and vaccines used by pregnant women</td>
<td>Pregnant between October 2009 through April 2012</td>
<td>1,032 (987)</td>
<td>2009 pandemic OR seasonal post-pandemic (TIIV; 2009–12)</td>
<td>SAB, stillbirths, PTB, SGA; congenital anomalies</td>
</tr>
<tr>
<td>Conlin et al., 2013</td>
<td>Because influenza vaccination is compulsory for active-duty U.S. military personnel, all pregnancies among military women actively serving during the 2009–2010 vaccination campaign had a high likelihood of exposure to this novel vaccine. We used data from this large cohort of women who received pandemic H1N1 vaccination during pregnancy to examine the affect of this vaccine on maternal and newborn health outcomes.</td>
<td>Pregnant between 1 October 2008 and 30 June 2009 (unexposed) or 1 October 2009 and 30 June 2010 (exposed)</td>
<td>17,936 (16,194)</td>
<td>2009 pandemic vaccine Pre-pandemic seasonal (TIIV; 2008–9)</td>
<td>SAB, PTB, congenital anomalies</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Recruitment period</td>
<td>Number of women (number of infants)</td>
<td>Interventions compared</td>
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<tr>
<td>Richards et al., 2013&lt;sup&gt;76&lt;/sup&gt;</td>
<td>To assess associations between maternal H1N1 influenza immunization and third-trimester preterm birth, low birth weight (LBW), and SGA within a managed care organization population.</td>
<td>Pregnant in third trimester from 26 April 2009 to 17 April 2010, with a live birth</td>
<td>3,236 (3,327)</td>
<td>2009 pandemic with or without 2009–10 seasonal (TIIV)</td>
<td>PTB, LBW, SGA</td>
</tr>
<tr>
<td>Yamada et al., 2012&lt;sup&gt;82&lt;/sup&gt;</td>
<td>To estimate the numbers of pregnant women that contracted flu, how many women took antiviral drugs for prophylaxis or treatment, and how effective vaccination for pandemic (H1N1) 2009 had been</td>
<td>Births from 1 December 2009 to 31 May 2010</td>
<td>7,328 (NA)</td>
<td>2009 pandemic with or without 2009–10 seasonal (TIIV)</td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Deinard et al., 1981&lt;sup&gt;93&lt;/sup&gt;</td>
<td>To learn whether exposure to the vaccine during pregnancy would have a measurable, deleterious effect on the mother's health, on the outcome of pregnancy, or on the health of her infant through the first 6-8 weeks of life.</td>
<td>During pregnancy, dates not reported</td>
<td>706 (675)</td>
<td>Monovalent inactivated ether-split-virion vaccine (Influenza A/New Jersey/8/76) (Parke, Davis and Company or Wyeth Laboratories) OR purified, concentrated whole virus vaccine (Merck Sharp and Dohme or Merrell-National Laboratories)</td>
<td>SAB, stillbirth, PTB, congenital anomalies</td>
</tr>
</tbody>
</table>

H1N1 = 2009 H1N1 pandemic influenza A virus (“swine flu”); IIV = inactivated influenza vaccine; LBW = low birthweight; NR = not reported; PTB = preterm birth; QIIV = quadrivalent inactivated influenza vaccine; SAB = spontaneous abortion; SAE = serious adverse events; SGA = small for gestational age; TIIV = trivalent inactivated influenza vaccine.
Supplement Table 3. Characteristics of three case-control studies evaluating influenza vaccines other than seasonal influenza vaccines, sorted by vaccine exposure evaluated, included in the systematic review of the safety of influenza vaccination during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Recruitment period</th>
<th>Number of women (number of infants)</th>
<th>Case definitions of interest</th>
<th>Exposure definition and windows</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies evaluating exposure to 2009 H1N1 Pandemic vaccine (n = 2)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Coenders et al., 2015</strong></td>
<td>To evaluate a possible association between the H1N1/09 vaccinations and the occurrence of PE and/or IUGR by investigating whether women with pre-eclampsia and/or intrauterine growth restriction were more or less likely to be vaccinated, compared to healthy controls</td>
<td>Pregnancies between 9 November 2009 and 26 February 2010, that were due up to 19 November 2010</td>
<td>501</td>
<td>SGA</td>
<td>2009 H1N1 monovalent adjuvanted vaccine any time during pregnancy</td>
</tr>
<tr>
<td><strong>Huang et al., 2014</strong></td>
<td>To examine the association between maternal H1N1 vaccination and spontaneous abortion (SAB) or adverse fetal outcomes in Taiwan</td>
<td>Live birth between 1 November 2009 and 30 September 2010</td>
<td>18,970</td>
<td>Stillbirth, PTB, LBW, SGA, congenital anomalies</td>
<td>2009 H1N1 monovalent nonadjuvanted and MF59-adjuvanted vaccines during first trimester, or during second or third trimester</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Recruitment period</td>
<td>Number of women (number of infants)</td>
<td>Case definitions of interest</td>
<td>Exposure definition and windows</td>
</tr>
<tr>
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<tr>
<td>Louik et al., 2013&lt;sup&gt;1&lt;/sup&gt;</td>
<td>To evaluate the risks and relative safety of the pH1N1 vaccine with respect to preterm delivery and birth defects using data from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)</td>
<td>During the 2009-10 pandemic vaccine season or 2010-11 seasonal vaccine season</td>
<td>3,865</td>
<td>Congenital anomalies</td>
<td>H1N1 monovalent or TIIV any time during pregnancy, and during the first trimester,</td>
</tr>
</tbody>
</table>

LBW = low birthweight; SAB = spontaneous abortion; SGA = small for gestational age; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; TIIV = trivalent inactivated influenza vaccine.
9. Findings for studies including both TIIIV and 2009 pandemic vaccine

Several studies combined seasonal vaccine (pre- and/or post-pandemic) with 2009 pandemic vaccine to form the exposed group of women compared to no vaccine, including Getahun et al., 2019; Kharbanda et al., 2017; Shakib et al., 2016; Cantu et al., 2013; Chambers et al., 2013; Louik et al., 2013; Richards et al., 2013; and Yamada et al., 2012. Characteristics of these studies have been reported in Supplement Tables 2 and 3 in Section 8 above. The supplemental Excel spreadsheets for detailed information regarding study methods, population characteristics, and findings.

10. Findings for other pandemic influenza vaccines

One cohort study evaluated the effects of a monovalent vaccine for the 1976 influenza A/New Jersey/8/76 strain and reported raw data for several birth outcomes. No analyses were reported. Characteristics of this study have been reported in Supplement Table 2 in Section 8 above. Please refer to the supplemental Excel spreadsheets for detailed information regarding study methods, population characteristics, and findings.

11. Findings for pandemic influenza vaccine vs pre-pandemic seasonal vaccine

Two studies evaluated non-standard vaccine comparisons and reported safety outcomes:

- Conlin et al., 2013: 2009 pandemic vaccine vs pre-pandemic seasonal vaccine
- Cleary et al., 2014: 2009 pandemic vaccine adjuvanted (Pandemrix) and non-adjuvanted (Celvapan) vs pre-pandemic seasonal vaccine

The study by Cleary et al. also reported 2009 pandemic vaccine vs no vaccine during the pandemic period and has been included in syntheses in Supplement Section 8 above. Characteristics of the two studies have been reported in Supplement Table 2 in Section 8 above. Please refer to the supplemental Excel spreadsheets for detailed information regarding study methods, population characteristics, and findings.
12. List of studies excluded at full-text screening, with reasons for exclusion

The citations of studies screened in full text during the original review (i.e., both RCTs and observational studies) and excluded for one or more reasons are detailed below. Citations have been grouped according to the reason for exclusion. RCTs that were included in the original review and excluded for the current safety review have been listed separately.

RCTs included in the original review


No full text
Maternal H1N1 vaccination associated with improved foetal and neonatal outcomes. Australian Journal of Pharmacy 2012. 93 (1111) 78-


Language not English or French

Anonymous. Aktuelle Urologie 2018. 49 (5) 389-.


Berlin, Maths. [Disinformation about the risks of adverse effect for children and fetuses of thiomersal in the vaccine]. Lakartidningen 2009. 106 (52) 3521-.

Bruhn, C. Flu vaccination: Risk of stillbirths is not increased. Pregnant women can be vaccinated against influenza. Deutsche Apotheker Zeitung 2013. 153 (7) 30-31.


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Galindo Santana, Belkys Maria, Pelaez Sanchez, Otto Reinaldo, Galindo Sardina, Miguel Angel, Leon Villafuerte, Milagros, Concepcion Diaz, Damarys, Estruch Rancano, C. Luis, Martinez Sanchez, Raydel, and Santin Pena, Manuel. [Active surveillance of adverse effects of Pandemrix vaccine to prevent influenza A(H1N1) in Cuba]. Revista cubana de medicina tropical 2011. 63 (3) 231-238.


Herrera, Gomez A. SAFETY AND EFFICACY OF INFLUENZA VACCINE IN PREGNANCY. Revista de enfermeria (Barcelona, Spain) 2015. 38 (2) 38-41.


Krandick, G. Child health after influenza vaccination during pregnancy. [German]. Monatsschrift fur Kinderheilkunde 2020. 168 (11) 975-976-.

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Maesschalck, J. Influenza vaccines and their evidenced based efficacy. Farmaceutisch Tijdschrift voor Belgie 2010. 87 (3) 66-74.


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Red. First influenza vaccine for infants under 6 months old. MMW-Fortschritte der Medizin 2019. 161 (16) 65-.


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No women vaccinated during pregnancy

H1N1 and this flu season. The pandemic may be over, but the virus is still around, and children, young adults, and pregnant women are susceptible. Harvard health letter 2010. 36 (2) 1-2.


M. Influenza epidemiology, vaccine coverage and vaccine effectiveness in sentinel Australian hospitals in 2013: the Influenza Complications Alert Network. Communicable diseases intelligence quarterly report 2014. 38 (2) E143-E149.


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Hauge, S. H., Bakken, I. J., de Blasio, B. F., Haberg, S. E. Risk conditions in children hospitalized with influenza in Norway, 2017-2019. BMC Infectious Diseases 2020. 20 (1) 769-


Kelly, H., Carcione, D., Dowse, G. K., and Effler, P. The vaccine-attributable risk for febrile convulsions following influenza vaccine. Pediatric Infectious Disease Journal 2012. 31 (7) 792--


Lara, A. N., Miyaji, K. T., Ibrahim, K. Y., Lopes, M. H., Sartori, A. M. C. Adverse events following yellow fever vaccination in immunocompromised persons. Revista do Instituto de Medicina Tropical de Sao Paulo 2021. 63 (1) e13--


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Tinnion, R. J. and Berrington, J. E. Flu vaccination for ex-preterms and infants under 6 months--are we getting it right? Archives of disease in childhood 2010. 95 (5) 400-401.


Not an eligible study design


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Flu vaccination during late pregnancy not associated with autism risk. Clinical Pharmacist 2017. 9 (2).

Flu vaccination in pregnancy protects both mothers and babies. Community practitioner : the journal of the Community Practitioners’ & Health Visitors’ Association 2016. 89 (1) 7-.


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Gabutti, G., Conforti, G., Tomasi, A., Kuhdari, P., Castiglia, P., Prato, R., Memmini, S., Azzari, C., Rosati, G. V., and Bonanni, P. Why, when and for what diseases pregnant and new mothers "should" be vaccinated. Human Vaccines and Immunotherapeutics 2017. 13 (2) 283-290.


Granwehr, B. P. Influenza immunisation during pregnancy reduced influenza in infants and respiratory illness in mothers. Evidence-Based Medicine 2009. 14 (2) 55-.


Hooker, B. S. Influenza vaccination in the first trimester of pregnancy and risk of autism spectrum disorder: To the editor. JAMA pediatrics 2017. 171 (6) 600-.

Horner, I., Nanan, R., and Liu, A. Influenza vaccination of pregnant women and protection of their infants. The New England journal of medicine 2014. 371 (24) 2340-.


Huang, Wan Ting, Chen, Wan Chin, Teng, Hwa Jen, Huang, Wei L., Huang, Yu Wen, Hsu, Chien Wen, and Chuang, Jen Hsiang. Adverse events following pandemic A (H1N1) 2009 monovalent vaccines in pregnant women--Taiwan, November 2009-August 2010. PloS one 2011. 6 (8) e23049-.


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Zuccotti, Gianvincenzo, Pogliani, Laura, Pariani, Elena, Amendola, Antonella, and Zanetti, Alessandro. Transplacental antibody transfer following maternal immunization with a pandemic 2009 influenza A(H1N1) MF59-adjuvanted vaccine. JAMA 2010. 304 (21) 2360-2361.

**No eligible intervention**


Toback, Seth L., Beigi, Richard, Tennis, Patricia, Sifakis, Frangiscos, Calingaert, Brian, and Ambrose, Christopher S. Maternal outcomes among pregnant women receiving live attenuated influenza vaccine. Influenza and other respiratory viruses 2012. 6 (1) 44-51.

**No valid comparator**


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**No safety outcomes**


Amin, A. B., Nunes, M. C., Tapia, M. D., Madhi, S. A., Cutland, C. L., Wairagkar, N., Omer, S. B., for, Bmgf Supported Maternal Influenza Immunization Trials Investigators Group. Immunogenicity of influenza vaccines administered to pregnant women in randomized clinical trials in Mali and South Africa. Vaccine 2020. 38 (41) 6478-6483-.

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Other exclusion reason


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Shah, Shetal I., Turcotte, Frances, and Meng, Hong Dao. Influenza vaccination rates of expectant parents with neonatal intensive care admission. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 2008. 21 (10) 752-757.


Zerbo, Ousseny, Qian, Yinge, Yoshida, Cathleen, Fireman, Bruce H., Klein, Nicola P., and Croen, Lisa A. Association Between Influenza Infection and Vaccination During Pregnancy and Risk of Autism Spectrum Disorder. JAMA pediatrics 2017. 171 (1) e163609-.
### 13. Evidence Maps

**Supplement Table 4. Safety outcomes reported in cohort studies included in a systematic review of the safety of influenza vaccination during pregnancy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Preterm birth</th>
<th>Spontaneous abortion</th>
<th>Stillbirth</th>
<th>Small for gestational age</th>
<th>Congenital anomalies</th>
<th>Maternal serious adverse events</th>
<th>Low birth weight</th>
<th>Fetal death OR combined fetal and perinatal mortality</th>
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<tbody>
<tr>
<td>McHugh et al., 2019&lt;sup&gt;42&lt;/sup&gt;</td>
<td>&lt; 37 weeks; stratified by trimester of vaccination</td>
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<tr>
<td>McHugh et al., 2019&lt;sup&gt;43&lt;/sup&gt;</td>
<td>&gt; 20 and &lt; 37 weeks, and &gt; 400 g</td>
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<tr>
<td>Singh et al., 2019&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Definition not reported</td>
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<tr>
<td>Ohfuji et al., 2018&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Raw demographic data reported</td>
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<td>Raw demographic data reported</td>
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<tr>
<td>Study</td>
<td>Preterm birth</td>
<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
<td>Maternal serious adverse events</td>
<td>Low birth weight</td>
<td>Fetal death OR combined fetal and perinatal mortality</td>
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<tr>
<td>Arriola et al., 2017&lt;sup&gt;46&lt;/sup&gt;</td>
<td>for 22 to 36 weeks</td>
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<td></td>
<td>diagnosed up to 5–7 months of age</td>
<td>data reported for &lt; 2500 g</td>
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<tr>
<td>McHugh et al., 2017&lt;sup&gt;47&lt;/sup&gt;</td>
<td>&lt; 37 weeks; stratified by trimester of vaccination</td>
<td></td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (Intergrowth); stratified by trimester of vaccination</td>
<td></td>
<td>&lt; 2500 g; stratified by trimester of vaccination; liveborn at any gestational age</td>
<td>&lt; 1000, &lt; 1500, and &lt; 2500 g; liveborn only; gestational age not reported</td>
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<tr>
<td>Zerbo et al., 2017&lt;sup&gt;48&lt;/sup&gt;</td>
<td>&lt; 37 weeks</td>
<td>&lt; 5&lt;sup&gt;th&lt;/sup&gt; and &lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (Fenton infant growth chart);</td>
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<td>&lt; 2500 g; liveborn ≥ 24 weeks</td>
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<tr>
<td>Chambers et al., 2016&lt;sup&gt;49&lt;/sup&gt;</td>
<td>&lt; 37 weeks; stratified by trimester of vaccination</td>
<td>&lt; 20 weeks; sensitivity analysis of first trimester vaccination</td>
<td>≥ 20 weeks; sensitivity analysis of first trimester vaccination</td>
<td></td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (NCHS 2000 growth curves or Lubchenko); measured according to weight, head circumference, or length; stratified by trimester of vaccination</td>
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<td>Study</td>
<td>Preterm birth&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
<td>Maternal serious adverse events</td>
<td>Low birth weight</td>
<td>Fetal death OR combined fetal and perinatal mortality</td>
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<td>Olsen et al., 2016&lt;sup&gt;10&lt;/sup&gt;</td>
<td>&lt; 37 weeks; stratified by trimester of vaccination and sensitivity analysis of timing with respect to the influenza season (during high and low influenza activity)</td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile of study population; sensitivity analysis of timing with respect to the influenza season (during high and low influenza activity)</td>
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<td>Stillbirth and early neonatal death; during pregnancy and up to 7 days of age; year-round influenza activity</td>
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<td>Regan et al., 2016a&lt;sup&gt;31&lt;/sup&gt;</td>
<td>≥ 20 weeks (all infants, preterm infants only, full-term infants only); all infant analysis stratified by time at risk with respect to the influenza season (before, during, after, and all year)</td>
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<td>Yamada et al., 2015&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>Ahrens et al., 2014&lt;sup&gt;14&lt;/sup&gt;</td>
<td>&lt; 37 weeks; stratified by trimester of vaccination; sensitivity analysis of 2009-10 season only</td>
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<td></td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile [American distribution 1999-2000]; stratified by trimester of vaccination; sensitivity analysis of 2009-10 season only</td>
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<td>Legge et al., 2014&lt;sup&gt;14&lt;/sup&gt;</td>
<td>&lt; 37 weeks; sensitivity analysis excluding deliveries occurring during the peak vaccination periods</td>
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<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile [reference not reported]</td>
<td>&lt; 2500 g; all births &gt; 20 gestational weeks; sensitivity analysis of full-term infants only</td>
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<td>Nordin et al., 2014&lt;sup&gt;15&lt;/sup&gt;</td>
<td>≤ 32, ≤ 34, and &lt; 37 weeks; stratified by trimester of vaccination</td>
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<td>&lt;5&lt;sup&gt;th&lt;/sup&gt; and &lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile [American standard by Oken]; stratified by trimester of vaccination</td>
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<tr>
<td>Study</td>
<td>Preterm birth&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
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<td>Adedinsewo et al., 2013&lt;sup&gt;6&lt;/sup&gt;</td>
<td>&lt; 37 completed weeks; stratified by periods of influenza activity (all, pre, least local, least regional, widespread, and putative influenza period)</td>
<td></td>
<td></td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (American standard by Oken); stratified by periods of influenza activity (all, pre, least local, least regional, widespread, and putative influenza period)</td>
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<td>Within 42 days of vaccination</td>
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<td>Dodds et al., 2012&lt;sup&gt;8&lt;/sup&gt;</td>
<td>&lt; 37 weeks</td>
<td></td>
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<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile of study population</td>
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<td>&lt; 2500 g; all infants; &gt; 20 weeks; sensitivity analysis among full-term infants only</td>
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<td>Sheffield et al., 2012&lt;sup&gt;9&lt;/sup&gt;</td>
<td>≤ 31 and ≤ 36 weeks</td>
<td>≥ 500 g; stratified by trimester of vaccination</td>
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<td>Diagnosed from birth to discharge/death; all births; stratified by trimester of vaccination</td>
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<td>&lt; 3&lt;sup&gt;rd&lt;/sup&gt; and &lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile; all births included</td>
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<td>Study</td>
<td>Preterm birth*</td>
<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
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<td>Eick et al., 2011&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>Omer et al., 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>&lt; 37 weeks; stratified by periods of influenza activity (all, pre, least local, least regional, widespread, and putative influenza period)</td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (American standard by Oken); stratified by periods of influenza activity (all, pre, least local, least regional, widespread, and putative influenza period)</td>
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<td>Munoz et al., 2005&lt;sup&gt;58&lt;/sup&gt;</td>
<td>&lt; 37 weeks</td>
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<td>Black et al., 2004&lt;sup&gt;53&lt;/sup&gt;</td>
<td>&lt; 37 weeks</td>
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</table>

**Studies comparing 2009 H1N1 pandemic vaccine to no vaccine (or no H1N1 vaccine)**
<table>
<thead>
<tr>
<th>Study</th>
<th>Preterm birth</th>
<th>Spontaneous abortion</th>
<th>Stillbirth</th>
<th>Small for gestational age</th>
<th>Congenital anomalies</th>
<th>Maternal serious adverse events</th>
<th>Low birth weight</th>
<th>Fetal death OR combined fetal and perinatal mortality</th>
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<tr>
<td>Ludvigsson et al., 2016&lt;sup&gt;44&lt;/sup&gt;</td>
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<td>Vazquez-Benitez et al., 2016&lt;sup&gt;4&lt;/sup&gt;</td>
<td>22 to 37 weeks; stratified by trimester of vaccination</td>
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<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (US national average); stratified by trimester of vaccination</td>
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<td>Baum et al., 2015&lt;sup&gt;45&lt;/sup&gt;</td>
<td>&lt; 28 and 28 to 36 weeks; stratified by trimester of vaccination</td>
<td>≥ 22 weeks; stratified by trimester of vaccination</td>
<td>&gt; 2 SD below Finnish mean; stratified by trimester of vaccination</td>
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<td>&lt; 1500 and 1500 to 2499 g; stratified by trimester of vaccination; live or stillborn at any gestational age</td>
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<td>Fabiani et al., 2015&lt;sup&gt;46&lt;/sup&gt;</td>
<td>&lt; 32 and &lt; 37 weeks</td>
<td>≥ 22 weeks</td>
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<td>Diagnosed at birth and 0 to 6 months of age; full-term live births only; second or third trimester vaccination</td>
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<td>&lt; 1500 and &lt; 2500 g; liveborn at full-term only</td>
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<tr>
<td>Ludvigsson et al., 2015&lt;sup&gt;47&lt;/sup&gt;</td>
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<td>Fetal death during pregnancy; stratified by</td>
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<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
<td>Maternal serious adverse events</td>
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<td>van der Maas et al., 2015</td>
<td>&lt; 37 weeks</td>
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<td>&lt; 10th percentile (Dutch average)</td>
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<td>Stillbirth and early neonatal death; time at risk outside and during the influenza season</td>
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<tr>
<td>Beau et al., 2014</td>
<td>&lt; 37 completed weeks; sensitivity analysis of singleton births only</td>
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<td>&gt; 2 SD below the French reference weight mean</td>
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<td>All-cause pregnancy loss</td>
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<td>Cleary et al., 2014</td>
<td>&lt; 32 and &lt; 37 weeks</td>
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<td></td>
<td>&lt; 10th percentile (<a href="http://www.gestation.net">www.gestation.net</a>)</td>
<td>Diagnosed at birth; unclear if fetal deaths included; first trimester and any trimester vaccination</td>
<td></td>
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<td>Stillbirth and early neonatal death; from 24 gestational weeks to 7 days of age; time at risk outside and during the influenza season</td>
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<td>Study</td>
<td>Preterm birth</td>
<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
<td>Maternal serious adverse events</td>
<td>Low birth weight</td>
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<tr>
<td>Ma et al., 2014(^1)</td>
<td>Definition not reported; sensitivity analysis amongst women with ILI</td>
<td>Definition not reported; sensitivity analysis amongst women with ILI</td>
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<td></td>
<td>Stillbirth and early neonatal death; during pregnancy and up to 7 days of age; time at risk outside and during the influenza season; sensitivity analysis excluding all events occurring within 14 days of vaccination/matched time</td>
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<tr>
<td>Trotta et al., 2014(^2)</td>
<td>&gt; 180 days; sensitivity analysis excluding all events occurring within 14 days of vaccination/matched time</td>
<td></td>
<td>&lt; 10(^{th}) percentile of study population; sensitivity analysis excluding all events occurring within 14 days of vaccination/matched time</td>
<td></td>
<td>Diagnosed from birth to discharge; all births between 23 and 45 weeks; second or third trimester vaccination; sensitivity analysis excluding all events occurring within 14 days of vaccination/matched time</td>
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<td>Stillbirth and early neonatal death; during pregnancy and up to 7 days of age; time at risk outside and during the influenza season; sensitivity analysis excluding all events occurring within 14 days of vaccination/matched time</td>
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<td>Cantu et al., 2013(^3)</td>
<td>&lt; 37 weeks; stratified by pregnancy risk level (all, high, low)</td>
<td>&lt; 20 weeks</td>
<td>≥ 20 weeks</td>
<td>&lt; 10(^{th}) percentile (Brenner’s standard); stratified by pregnancy risk level (all, high, low)</td>
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<td>&lt; 2500 g; stratified by pregnancy risk level (all, high, low)</td>
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<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
<td>Maternal serious adverse events</td>
<td>Low birth weight</td>
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<td>Håberg et al., 2013²⁴</td>
<td>&lt; 37 completed weeks</td>
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<td>&lt; 2500 g; full-term only (&gt; 27 weeks); live/stillborn not reported</td>
<td>Miscarriage and stillbirth</td>
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<td>Ludvigsson et al., 2013⁷⁵</td>
<td>&lt; 37 completed weeks; stratified by trimester of vaccination</td>
<td>&lt; 10th percentile of study population; stratified by trimester of vaccination</td>
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<td>&lt; 2500 g; stratified by trimester of vaccination; liveborn only; gestational age not reported</td>
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<td>Richards et al., 2013²⁶</td>
<td>27 to 36, 27 to 33, and 34 to 36 weeks</td>
<td>&lt; 10th percentile (American standard by Oken)</td>
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<td>&lt; 2500 g; liveborn only; gestational age not reported</td>
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<td>Rubinstein et al., 2013⁷⁷</td>
<td>&lt; 37 weeks</td>
<td>&gt; 22 weeks</td>
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<td>&lt; 1500 and &lt; 2500 g; live/stillborn and gestational age not reported</td>
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<td>Fell et al., 2012²⁸</td>
<td>&lt; 32 and &lt; 37 weeks</td>
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<td>&lt; 3rd and &lt; 10th percentile (Canadian reference)</td>
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<td>Stillbirth</td>
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<td>Congenital anomalies</td>
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<td>Fetal death OR combined fetal and perinatal mortality</td>
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<td>Heikkinen et al., 2012$^{79}$</td>
<td>Definition not reported</td>
<td>&lt; 22 weeks</td>
<td>&gt; 22 weeks</td>
<td>Diagnosed up to 3 months of age; all births; any trimester vaccination</td>
<td>Definition not reported; all births included</td>
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<td>Källén et al., 2012$^{80}$</td>
<td>&lt; 37 weeks; stratified by gestational week of vaccination (weeks 1–19, 20–26, and 27–36)</td>
<td>Definition not reported</td>
<td>&gt; 2 SD below expected weight (Swedish registry)</td>
<td>Diagnosed at birth; all births during pandemic; week 1–9 vaccination and first trimester vaccination</td>
<td>&lt; 2500 g; all singleton births included</td>
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<td>Launay et al., 2012$^{81}$</td>
<td>&lt; 37 weeks</td>
<td>Death during labour but not before</td>
<td>Unclear when diagnosed; possibly all births; second or third trimester vaccination</td>
<td>&lt; 2500 g; all births included</td>
<td>SAB and stillbirths defined as (1) deaths before labour only and (2) deaths before and during labour</td>
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<td>Lin et al., 2012$^{82}$</td>
<td>&lt; 35 and 35 to 37 weeks</td>
<td>Definition not reported</td>
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<td>Diagnosed up to 2 months of age; unclear if stillbirths included; any trimester vaccination</td>
<td>&lt; 2500 g; all births included</td>
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<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
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<td>Pasternak et al., 2012&lt;sup&gt;2a&lt;/sup&gt;</td>
<td>&lt; 37 completed weeks; stratified by trimester of vaccination</td>
<td>&lt; 32 and 33 to 37 completed weeks</td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile of study population; stratified by trimester of vaccination</td>
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<td>Pasternak et al., 2012&lt;sup&gt;2a&lt;/sup&gt;</td>
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<td>&gt; 22 weeks</td>
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<td>Sammon et al., 2012&lt;sup&gt;2b&lt;/sup&gt;</td>
<td>9 to 12 weeks and 13 to 24 weeks, separately; exposure windows any time prior to event and within 28 days of event</td>
<td>&gt; 25 weeks; exposure windows any time prior to event and within 28 days of event</td>
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<td>Mackenzie et al., 2011&lt;sup&gt;2c&lt;/sup&gt;</td>
<td>Definition not reported; stratified by trimester of vaccination</td>
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<sup>1</sup>Defined as birth before 37 completed weeks of gestation.  
<sup>2a</sup>Stratified by trimester of vaccination.  
<sup>2b</sup>Stratified by gestational age.  
<sup>2c</sup>Stratified by gestational age and birth weight.
<table>
<thead>
<tr>
<th>Study</th>
<th>Preterm birth</th>
<th>Spontaneous abortion</th>
<th>Stillbirth</th>
<th>Small for gestational age</th>
<th>Congenital anomalies</th>
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<td>Getahun et al., 2019&lt;sup&gt;87&lt;/sup&gt;</td>
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<td>Kharbanda et al., 2017&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Definition not reported; stratified by trimester of vaccination</td>
<td>≥ 20 weeks; stratified by trimester of vaccination</td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile of study population; stratified by trimester of vaccination</td>
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<td>Specific congenital anomalies diagnosed up to 6 months of age</td>
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<td>Shakib et al., 2016&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Raw demographic data and definition not reported</td>
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**Studies evaluating interventions that were not purely seasonal (TIIV and/or QIIV) or 2009 H1N1 pandemic vaccine, or that compared to an unexposed group other than “no vaccine” or “no H1N1 vaccine”**
<table>
<thead>
<tr>
<th>Study</th>
<th>Preterm birth&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Spontaneous abortion</th>
<th>Stillbirth</th>
<th>Small for gestational age</th>
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<tbody>
<tr>
<td>Chambers et al., 2013&lt;sup&gt;20&lt;/sup&gt;</td>
<td>&lt; 37 completed weeks; stratified by trimester of vaccination; sensitivity analysis of 2009–2010 season only</td>
<td>&lt; 20 weeks; sensitivity analysis of first trimester vaccination</td>
<td>≥ 20 weeks; sensitivity analysis of first trimester vaccination</td>
<td>&lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile (American standard by CDC or Lubchenko); measured according to weight, head circumference, or length; stratified by trimester of vaccination</td>
<td>Diagnosed at birth; including all births and liveborn only; sensitivity analysis of prenatal testing for fetal anomaly (tested with normal result, no diagnosis of anomaly prior to enrolment); first trimester vaccination</td>
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<td>Conlin et al., 2013&lt;sup&gt;21&lt;/sup&gt;</td>
<td>&lt; 37 completed weeks</td>
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<td>Diagnosed at birth; liveborn only; adjusted for first trimester vaccination in model</td>
<td></td>
<td>Pregnancy loss based on ICD-9-CM diagnostic codes</td>
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<td>Yamada et al., 2012&lt;sup&gt;22&lt;/sup&gt;</td>
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<tr>
<td>Study</td>
<td>Preterm birth</td>
<td>Spontaneous abortion</td>
<td>Stillbirth</td>
<td>Small for gestational age</td>
<td>Congenital anomalies</td>
<td>Maternal serious adverse events</td>
<td>Low birth weight</td>
<td>Fetal death OR combined fetal and perinatal mortality</td>
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<tr>
<td>Deinard et al., 1981&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Definition not reported; stratified by trimester of vaccination</td>
<td>Definition not reported; stratified by trimester of vaccination</td>
<td>≥ 20 weeks; stratified by trimester of vaccination</td>
<td>Diagnosed from birth to discharge and up to 2 months of age; unclear if fetal deaths assessed; stratified by trimester of vaccination</td>
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<tr>
<td>MIIV New Jersey/8/76 vs No vaccine</td>
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<sup>a</sup> The definition of preterm birth was assumed to include only liveborn infants, unless otherwise stated.

CDC = Centers for Disease Control; ILI = influenza-like illness; MIIV = monovalent inactivated influenza vaccine; NCHS = National Centre for Health Statistics; QIIV = quadrivalent inactivated influenza vaccine; SAB = spontaneous abortion; SD = standard deviation; TIIV = trivalent inactivated influenza vaccine.
Supplement Table 5. Safety outcomes reported in case-control studies included in a systematic review of the safety of influenza vaccination during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Spontaneous abortion</th>
<th>Stillbirth</th>
<th>Preterm birth</th>
<th>Low birth weight</th>
<th>Small for gestational age</th>
<th>Congenital anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies comparing TIV and/or QIV to no vaccine</td>
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<tr>
<td>Panagiotakopoulos et al., 2020&lt;sup&gt;94&lt;/sup&gt;</td>
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<tr>
<td>Donahue et al., 2019&lt;sup&gt;95&lt;/sup&gt;</td>
<td>6 to &lt; 20 gestational weeks; exposure windows 1 to 28 days before SAB, 1 to 28 days after conception, and &gt; 28 days after conception</td>
<td>Fetal death ≥ 20 gestational weeks</td>
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<tr>
<td>Donahue et al., 2017&lt;sup&gt;96&lt;/sup&gt;</td>
<td>5 to &lt; 20 gestational weeks; exposure window: 1 to 28 days before SAB</td>
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<td>Louik et al., 2016&lt;sup&gt;97&lt;/sup&gt;</td>
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<td></td>
<td>Any major structural defects and specific anomalies reported separately; diagnosed from 0 to 6 months of age; exposure window: first trimester only</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Study</th>
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<th>Congenital anomalies</th>
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<tr>
<td>Irving et al., 2013&lt;sup&gt;98&lt;/sup&gt;</td>
<td>5 to 16 gestational weeks; exposure windows 1 to 28 days before SAB and anytime during pregnancy</td>
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<tr>
<td>Studies comparing 2009 H1N1 pandemic vaccine to no vaccine (or no H1N1 vaccine)</td>
<td>&lt;sup&gt;99&lt;/sup&gt;</td>
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<tr>
<td>Coenders et al., 2015&lt;sup&gt;99&lt;/sup&gt;</td>
<td>≥ 20 gestational weeks; exposure windows: first trimester only and second or third trimester combined; stratified by presence of adjuvant (all vaccines, adjuvanted, and non-adjuvanted)</td>
<td>&lt;sup&gt;99&lt;/sup&gt;</td>
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<td>Huang et al., 2014&lt;sup&gt;100&lt;/sup&gt;</td>
<td>≥ 20 gestational weeks; exposure windows: first trimester only and second or third trimester combined; stratified by presence of adjuvant (all vaccines, adjuvanted, and non-adjuvanted)</td>
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<td>Studies comparing a mix of seasonal (TIIV and/or QIIV) and monovalent 2009 H1N1 pandemic vaccine to no vaccine</td>
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<td>Louik et al., 2013&lt;sup&gt;101&lt;/sup&gt;</td>
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Studies comparing 2009 H1N1 pandemic vaccine to no vaccine (or no H1N1 vaccine)

- <sup>98</sup> Irving et al., 2013
- <sup>99</sup> Coenders et al., 2015
- <sup>100</sup> Huang et al., 2014
- <sup>101</sup> Louik et al., 2013

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<td>specific anomalies reported separately; diagnosed from 0 to 6 months of age; exposure window: first trimester only</td>
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QIV = quadrivalent inactivated influenza vaccine; SAB = spontaneous abortion; TIIV = trivalent inactivated influenza vaccine
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