


RESEARCH PAPER



The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review

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ABSTRACT

Pregnant women are at increased risk of morbidity and mortality from influenza and are recognized as a priority group for influenza vaccination. Despite this, uptake is often poor and one reason cited for this is concerns about safety. The objective of this study was to perform a systematic review of the safety of inactivated influenza vaccination (IIV) in pregnancy. Studies were included if they were: (i) observational or experimental design; (ii) included a comparator group comprising of unvaccinated pregnant women; (iii) comprised of either seasonal IIV or monovalent H1N1 IIV (including adjuvanted vaccines); and (iv) addressed one of the following outcomes: preterm birth (PTB), small for gestational age (SGA), fetal death (including stillbirth or spontaneous abortion), low birth weight (LBW) or congenital abnormalities. Two reviewers screened abstracts and titles and selected full texts for retrieval. Crude odds ratios were calculated from reported event rates, using binomial standard errors. Adjusted odds ratios, hazard ratios and relative rates were extracted as reported in each paper. After removal of duplicates and full text eligibility assessment, 40 studies remained. The aOR for PTB was 0.87 (0.78–0.96), for LBW 0.82 (0.76–0.89), congenital abnormality 1.03 (0.99–1.07), SGA 0.99 (0.94–1.04) and stillbirth 0.84 (0.65–1.08). This study contributes to the increasing body of safety data for IIV in pregnancy and reports a protective effect on PTB and LBW.

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Introduction



Severe pandemic H1N1 influenza infection has well-described adverse effects on pregnant women and pregnancy outcomes, which are preventable through vaccination. An association between milder seasonal influenza and severe maternal disease and poor birth outcomes is less clear. Influenza vaccination across all trimesters has been recommended since the 1960s¹ however uptake continued to be low until the 2009 H1N1 influenza pandemic. Despite pregnant women being nominated as a priority group for vaccination,² most studies suggest that uptake remains below 50%.³


More recently, data have suggested that in addition to maternal benefits, there are benefits for the fetus and neonate.⁴ The landmark study by Zaman et al demonstrated that infants born to vaccinated mothers were 63% less likely to have laboratory confirmed influenza in the first six months of life.⁵ More recently, there have been three randomized controlled trials published, reporting a vaccine efficacy against laboratory confirmed influenza in infants of vaccinated mothers under 6 months of age ranging from 30% to 43.1%.^{6–8}

One barrier to improving influenza vaccine uptake in pregnant women includes concerns regarding safety amongst consumers and healthcare providers. Consumer concerns

have been reported consistently across multiple studies.⁹ The language and content of the product information or product monograph makes it difficult to reconcile positive recommendation for vaccination in highly respected clinical guidelines and policy recommendations with information provided by the manufacturer. A published review by Proveaux et al reported on 96 separate influenza vaccines and found that 20 of these (21%) included language suggesting that official recommendations should be “considered”, half of the manufacturers suggest users consult a health care provider to determine whether the product should be given during pregnancy and only 10/98 product information suggested use during pregnancy.¹⁰ A subsequent study of 141 maternal health-care providers from 49 countries in all six World Health Organization (WHO) regions suggested that health-care providers perceive product information as contradicting WHO and national immunisation recommendations and that this could affect their decision to recommend the vaccine to pregnant women.¹¹

In 2011, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization asked the Global Advisory Committee on Vaccine Safety (GACVS) to review the evidence on safety of vaccination in pregnant and lactating women. This report included studies examining influenza

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 Supplemental data can be accessed at tandfonline.com/khvi

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vaccination in pregnancy and various outcome measures (including maternal morbidity and mortality, miscarriage/stillbirth, prematurity, small size for gestational age and congenital anomalies) and did not find any safety concerns.¹²

Since publication of the GACVS report in 2014, there have been five systematic reviews of influenza vaccine safety in pregnancy.¹³⁻¹⁷ Given maternal immunisation is such a rapidly evolving field, and uptake of influenza vaccine continues to be suboptimal, it is important to continue to review the safety data to be able to support policy recommendations and reassure both healthcare providers and consumers about the safety of vaccination during pregnancy. This systematic review includes five pregnancy outcomes of interest including small for gestational age which was not included in the previous cited systematic reviews, and includes new publications from the previous three years.

Methods

Literature search methods

Systematic literature searches were conducted by a medical librarian in key bibliographic databases including OVID Medline (1946-April Week 3 2017), OVID Embase (1974-Week 18 2017), Cochrane Library databases including Database of Systematic Reviews (Issue 5 of 12, May 2017), Central Register of Controlled Trials (Issue 4 of 12, April 2017), Database of Abstracts of Reviews of Effects (Issue 2 of 4, April 2015), NHS Economic Evaluation Database (Issue 2 of 4, April 2015) and Health Technology Assessments (Issue 4 of 4, October 2016 and SCOPUS (1823-May 2017). Publications after May 2017 were not included in this systematic review.

From search results, duplicates were removed and two independent reviewers screened all abstracts and titles. Full studies selected for retrieval were assessed by two independent reviewers prior to inclusion in the review. Studies that reported on outcomes in different cohorts (eg in different seasons, or using different vaccines) were treated as separate, independent studies.

Inclusion criteria

Studies were included if they were: (i) observational or experimental design (including cohort, case-control, cross-sectional, randomized controlled clinical trial); (ii) there was a comparator group comprising of unvaccinated pregnant women; (iii) the intervention comprised of either seasonal influenza vaccine or monovalent pandemic H1N1 influenza vaccine; (iv) the vaccine was adjuvanted or non adjuvanted and (v) if the study addressed one of the following outcomes: preterm birth (PTB), small for gestational age (SGA), fetal death (including stillbirth or spontaneous abortion), low birth weight (LBW) or congenital abnormalities.

Excluded studies

Case reports and case series were not included. Articles written in a language other than English were excluded.

Definitions related to outcomes of interest

The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project, published in 2016, sought to improve the quality of outcome data from clinical vaccine trials in pregnant women, with a specific focus on safety monitoring in low and middle-income countries.¹⁸ Twenty-one standardized case definitions for obstetric outcomes and neonatal outcomes were developed and standardized case definitions for preterm birth, stillbirth, congenital abnormalities, spontaneous abortion, small for gestational age and low birth weight have been published.¹⁹⁻²⁴

Preterm birth (PTB)

For this review PTB has been defined as any live birth prior to 37 completed gestational weeks.

Stillbirth and spontaneous abortion

Stillbirth refers to death of the fetus. However, miscarriage (spontaneous abortion) also refers to death of the fetus. There is no universally accepted definition of when a fetal death is called a stillbirth versus spontaneous abortion. In addition, limitations in capacity to use tools, such as ultrasound, to accurately determine gestational age can impact on the quality of data for this outcome measure. Existing definitions for stillbirth include > 20 weeks (USA CDC), > 22 weeks (WHO/ICD for general statistics and registration), > 22 weeks (European Medicines Agency), > 24 weeks (UK) and > 28 weeks (WHO/ICD for international comparison and reporting). The case definition determined by the Brighton Collaboration Stillbirth Working Group does not use a specific gestational age cut off to distinguish between miscarriage (spontaneous abortion) and stillbirth, but rather considers variability based on viability cut-offs in different settings.²⁰ For this review stillbirth was defined as after 22 weeks gestation and spontaneous abortion defined as prior to 22 weeks gestation.

Congenital abnormalities

For this review, we defined congenital abnormalities (also referred to as birth defects, congenital malformations or congenital anomalies) as a condition that developed *in utero*, was present at birth and can impact on the infant's health.²¹

Low birth weight

For this review we defined low birth weight as less than 2500 gm.

Small for gestational age

For this review we defined small for gestational age as weight below the 10th percentile for gestational age as assessed against a validated global, regional or local standard defined in the study.

Background rate of outcomes of interest

The source of the background rate used to compare the outcomes of interest for the calculations related to number needed to vaccinate was derived from the Australian National Perinatal Data collection published in 2018. This was chosen as it is a national dataset, therefore collecting data on all public and private births, including all indigenous and ethnic groups, all socioeconomic groups in a setting where 99.9% of women have at least one antenatal visit and only 0.3% of births occur outside of facilities. Background rates from a resource rich setting were selected to be comparable with the settings for the majority of included studies.

Data extraction and assessment of methodological quality

We developed a standard data collection form to extract study information including: study design, setting, time period, participants, vaccine type, timing of exposure per trimester if reported, comparator, outcome, definition of outcome used in the study, events in the vaccinated group, events in the comparator group, adjusted effect including upper and lower confidence interval limits.

Each reviewer independently assessed quality using the Newcastle-Ottawa Scale. This is a scale developed by the Cochrane review group on Effective Practice and Organisation of care to assess the quality of non-randomized studies to determine the potential for selection bias, information bias and residual confounding.²⁵ It is a nine point scale that evaluates studies on representativeness of the study population, selection of controls, ascertainment of exposure, baseline assessment, comparability of cohorts and assessment of outcome, duration of follow up and adequacy of follow up. Studies are assessed on the potential for selection bias (up to 4 stars), comparability (up to 2 stars) and exposure ascertainment (up to 3 stars). We deemed the most important potential confounder as maternal age. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to synthesise the overall quality of evidence and implications for practice.²⁶ This process provides a framework for summarizing evidence, assessing the quality of evidence and formulating recommendations. In assessing the quality of evidence, we downgraded quality based on all factors (risk of bias, inconsistency, indirectness, imprecision and publication bias).

Statistical analysis

Crude odds ratios for influenza vaccinated versus non influenza vaccinated cohorts for each outcome measure were calculated from reported event rates in each study, using binomial standard errors. Adjusted odds ratios, hazard ratios and relative rates were extracted as reported in each study. Outcomes were reported according to the most detailed information provided on trimester of exposure: first trimester, second trimester, and third trimester; second and third trimester together; or at any time during pregnancy. Pooled event rates were estimated using random effects

models. Forest plots were generated and pooled estimates were calculated using the metan module in Stata 14.2 (College Station, Texas, United States). The number needed to vaccinate (NNV), where p is the background rate and θ is the odds ratio, was calculated using the formula:

$$NNV = \frac{1 - p(1 - \theta)}{p(1 - p)(1 - \theta)}$$

Results

A total of 4160 publications were identified. After duplicates were removed 3900 records remained. Of these, 3729 records were excluded after abstract screening, leaving 171 records for full article eligibility assessment. In total, 131 full-text articles were excluded. The most common reasons for exclusion were: (i) the article was a review rather than a primary study ($n = 33$); (ii) the publication was an abstract with insufficient results to calculate an odds ratio ($n = 20$); (iii) there was no comparator ($n = 16$); (iv) the comparator was inappropriate for this review ($n = 12$); and (v) the publication was a letter that did not provide adequate information ($n = 11$). The remaining reasons for exclusion are listed in the PRISMA diagram (Figure 1).

Of the 40 included studies, 25 were retrospective cohort studies, 9 were prospective cohort studies, three were case control studies, two were cross sectional and one was a randomized controlled trial²⁷⁻⁶⁶ (Supplementary Table 1). Only 15 of 40 studies included vaccine brand-specific information, of which three used both adjuvanted and non-adjuvanted vaccines. No studies used quadrivalent influenza vaccine. All studies were conducted between 1976 and 2015. The majority of studies were conducted in high-income countries with the exception of South Africa, Laos, Taiwan, China and Argentina. The results for assessment of quality according to the Newcastle-Ottawa scale are in presented in Supplementary Table 2.

Preterm birth

In total, 26 studies included data on 184,305 women vaccinated during pregnancy (including 9,280 known to be vaccinated in the first trimester, 1,177 vaccinated in the second trimester, 11,314 vaccinated in either the second or third trimester, and 711 vaccinated in the third trimester). This included 173,131 women vaccinated during pregnancy in risk adjusted analyses (12 studies reporting adjusted odds ratios and 12 studies reporting adjusted relative risks or hazard ratios).

The estimated adjusted odds of preterm birth for women who received any influenza vaccine during pregnancy was 0.87 (0.78–0.96) (Figure 2). This reduced risk of preterm birth associated with vaccination equates to a number needed to benefit of 98 (one preterm birth would be prevented for every 98 women vaccinated), based on a background rate of preterm birth of 8.6%. The possible increased risk of preterm birth with first trimester vaccination is not statistically significant in the adjusted odds ratio and adjusted relative risk analyses, however the estimates are imprecise. The strength of evidence

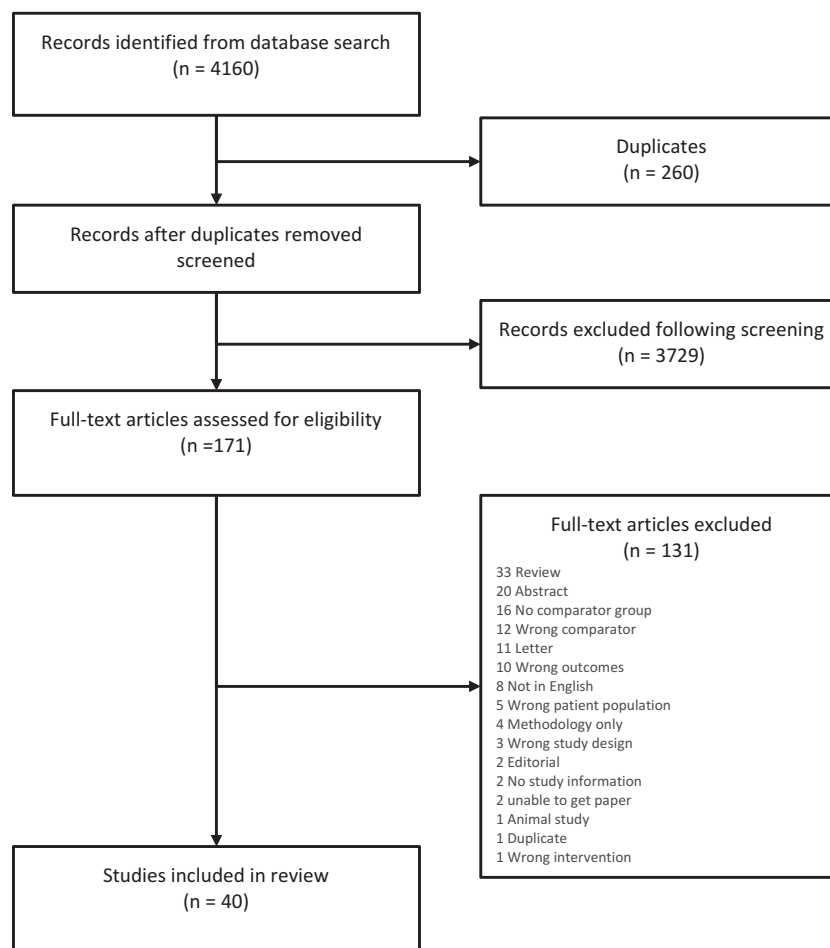


Figure 1. PRISMA diagram.
Flowchart of studies

was assessed as moderate; despite the inherent potential for bias associated with observational data, studies were generally consistent and provided a precise estimate of effect.

Low birth weight

In total, 12 studies included 84 314 women vaccinated during pregnancy (including 8169 known to be vaccinated in the first trimester). This included 81 609 women vaccinated during pregnancy in adjusted analyses (7 studies reporting adjusted odds ratios and 3 studies reporting adjusted relative risks or hazard ratios).

The estimated adjusted odds ratio of outcome was 0.82 (0.76–0.89) (Figure 3). This suggests a reduced risk of low birth weight associated with vaccination, with number needed to benefit of 96, based on a background rate of 6.2%. The strength of evidence was assessed as high; despite the inherent risk of bias associated with observational data, studies were consistent and provided a precise estimate effect.

Congenital abnormalities

In total, 12 studies included 169 828 women vaccinated during pregnancy (including 765 vaccinated in the first trimester, and 2548 vaccinated in the second or third trimesters). This

included 157,601 women vaccinated during pregnancy in risk adjusted analyses (7 studies reporting adjusted odds ratios and 2 studies reporting adjusted relative risks or hazard ratios).

For the 16 studies that looked at congenital abnormality as an outcome, only 5 performed an analysis including first trimester exposure as a stand-alone group not combined with any other trimesters of exposure. This is important given the highest risk period for congenital abnormality arising from teratogen exposure is thought to be during embryogenesis and early fetal development.

The estimated adjusted odds ratio of outcome was 1.03 (95% CI: 0.99–1.07) (Figure 4). This suggests no significant increase or decrease in the risk of congenital abnormalities associated with vaccination. Hypothetically, based on the upper limit of confidence interval and baseline incidence of 308 congenital abnormalities per 100,000 births, the number needed to harm is unlikely to be less than 5428. The strength of evidence was moderate; despite the inherent risk of bias associated with observational data, studies were generally consistent and provided a precise estimate of effect.

Small for gestational age

In total, 17 studies included 176 486 women vaccinated during pregnancy (including 8912 known to be vaccinated in the

Preterm birth

Adjusted OR of outcome

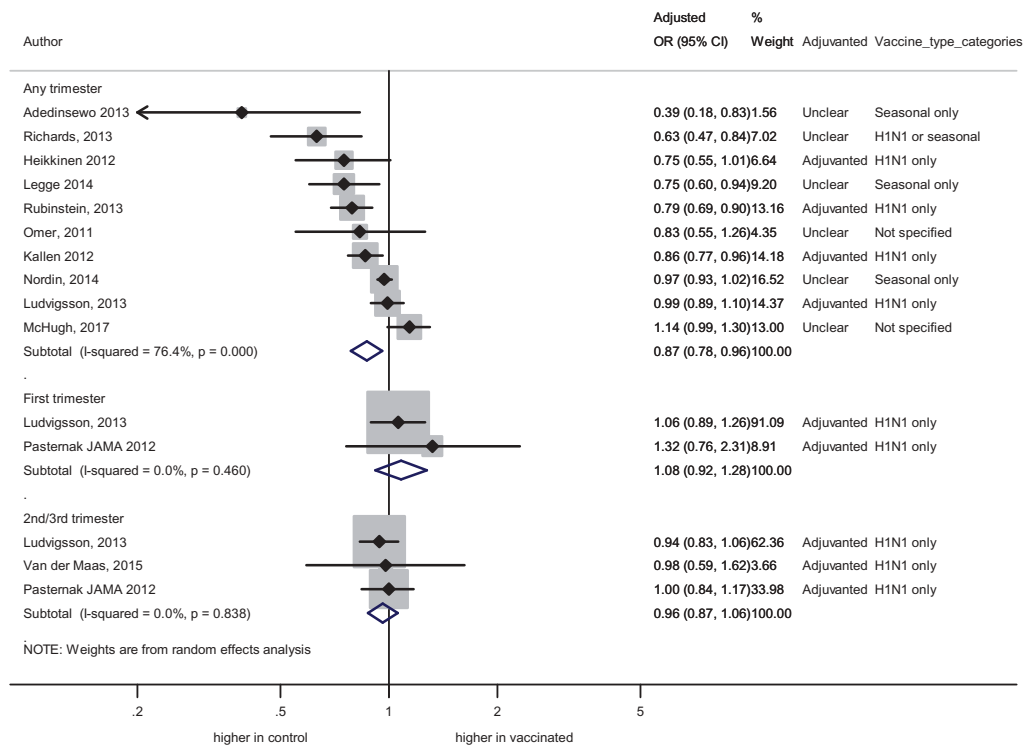


Figure 2. Preterm birth. Adjusted Odds Ratio

first trimester, 754 vaccinated in the second trimester, 7765 vaccinated in either the second or third trimester, and 431 vaccinated in the third trimester). This included 164,966 women vaccinated during pregnancy in risk-adjusted analyses (12 studies reporting adjusted odds ratios and 7 studies reporting adjusted relative risks or hazard ratios).

The estimated adjusted odds ratio of outcome was 0.99 (95% CI: 0.94–1.04) (Figure 5). This suggests no significant increase or decrease in the risk of small for gestation age births associated with vaccination. Hypothetically, based on the upper limit of the confidence interval and baseline risk of 9%, the number needed to harm is unlikely to be less than 444. The strength of evidence was low; in addition to the inherent risk of bias associated with observational data, studies were not completely consistent although the data provided a precise estimate of effect.

Fetal death

In total, 20 studies included 152,713 women vaccinated during pregnancy (including 8654 known to be vaccinated in the first trimester and 3385 vaccinated in either the second or third trimester) comparing the risk of stillbirth to the risk in unvaccinated pregnant women. This included 145,185 women vaccinated during pregnancy in risk-adjusted analyses. Additionally, eight studies included 6,471 women vaccinated during pregnancy comparing risk of spontaneous abortion to the risk in unvaccinated pregnant women.

Despite the smaller number of studies including spontaneous abortion as an outcome, the available data suggested an overall protective effect (crude OR 0.27, 95% CI: 0.14, 0.52). Three of the eight studies individually demonstrated a statistically significant reduction in spontaneous abortion.

The estimated adjusted odds ratio of stillbirth was 0.84 (95% CI: 0.65–1.08) (Figure 6). This suggests no significant increase or decrease in the risk of fetal death associated with vaccination. Based on the confidence intervals and baseline risk of 7 per 1000 births, the number needed to vaccinate to prevent one stillbirth is estimated at 900, and number needed to harm unlikely to be less than 3597. The strength of evidence was assessed as high; despite the inherent risk of bias associated with observational data, studies were consistent and provided a precise estimate of effect.

Adjuvanted versus non-adjuvanted vaccines

Results in studies that examined adjuvanted vaccines were similar for SGA (pooled adjusted OR 0.98, 95% CI: 0.93, 1.03); PTB (0.86, 95% CI: 0.77, 0.99), LBW (0.83, 95% CI: 0.75, 0.92), fetal death (0.84, 95% CI: 0.65, 1.08) and congenital abnormalities (1.02, 95% CI: 0.98, 1.06).

Discussion

The findings from this systematic review not only confirm the safety of influenza vaccination in pregnancy but provide

Low birth weight

Adjusted OR of outcome

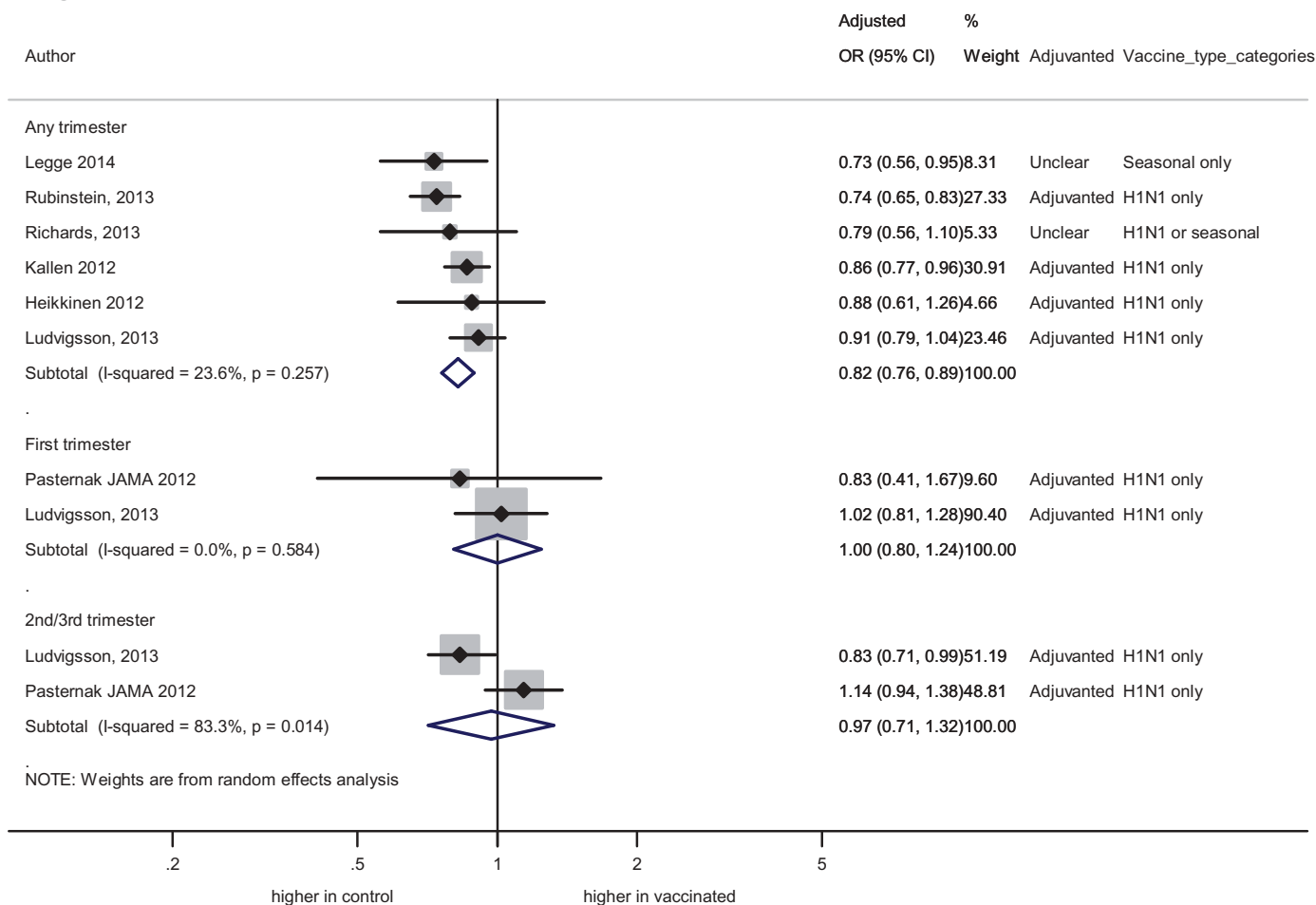


Figure 3. Low birth weight. Adjusted Odds Ratio

evidence to support a protective effect against preterm birth and low birth weight. Specifically, vaccination was not associated with an increase in preterm birth, low birth weight, small for gestational age newborns, congenital abnormalities, spontaneous abortion or stillbirth. This is based on multiple studies involving more than 100,000 pregnant women, with the exception of low birth weight ($n = 84314$ women) and spontaneous abortion ($n = 6471$ women).

In comparison to no influenza vaccination in pregnancy, we found high quality evidence that the use of inactivated influenza vaccine is associated with a reduction in incidence of low birth weight newborns, and no significant difference in the incidence of stillbirth. We found moderate quality evidence that the use of influenza vaccine is associated with reduction in preterm births and no difference in congenital abnormalities. We also found low quality evidence of the effect of influenza vaccination on spontaneous abortion, which suggested a protective effect, and on small for gestational age births which suggested no difference. We did not find any differences in the risk of adverse pregnancy outcomes when the analysis was restricted to adjuvanted influenza vaccines versus no vaccine.

Maternal immunisation is a rapidly evolving area. In comparison to previous systematic reviews published in 2015–2016,^{13–17} our manuscript includes small for gestational age as an outcome of interest, 40 publications along with a meta-analysis, and ten papers published between 2015–2017 (at closure of our search date). We also performed a sub-analysis examining adjuvanted vaccines versus no vaccine which was only included in one of the previous systematic reviews. Since undertaking our literature search (which ended May 2017), there have been a number of important publications which were not included but are worthy of mention. There have been two randomized controlled trials in pregnant women published which compared IIV to placebo.^{6,7} Specifically the study by Nunes and colleagues,⁶ reported a vaccine efficacy of 43% against all-cause acute lower respiratory tract infection and hospitalization in the first 6 months of life and no difference in rates of preterm birth and low birth weight between the vaccinated and unvaccinated groups. This study was conducted in South Africa and included 1026 vaccinated women. In the study by Steinhoff,⁷ influenza vaccination reduced maternal febrile influenza-like

Congenital anomalies

Adjusted OR of outcome

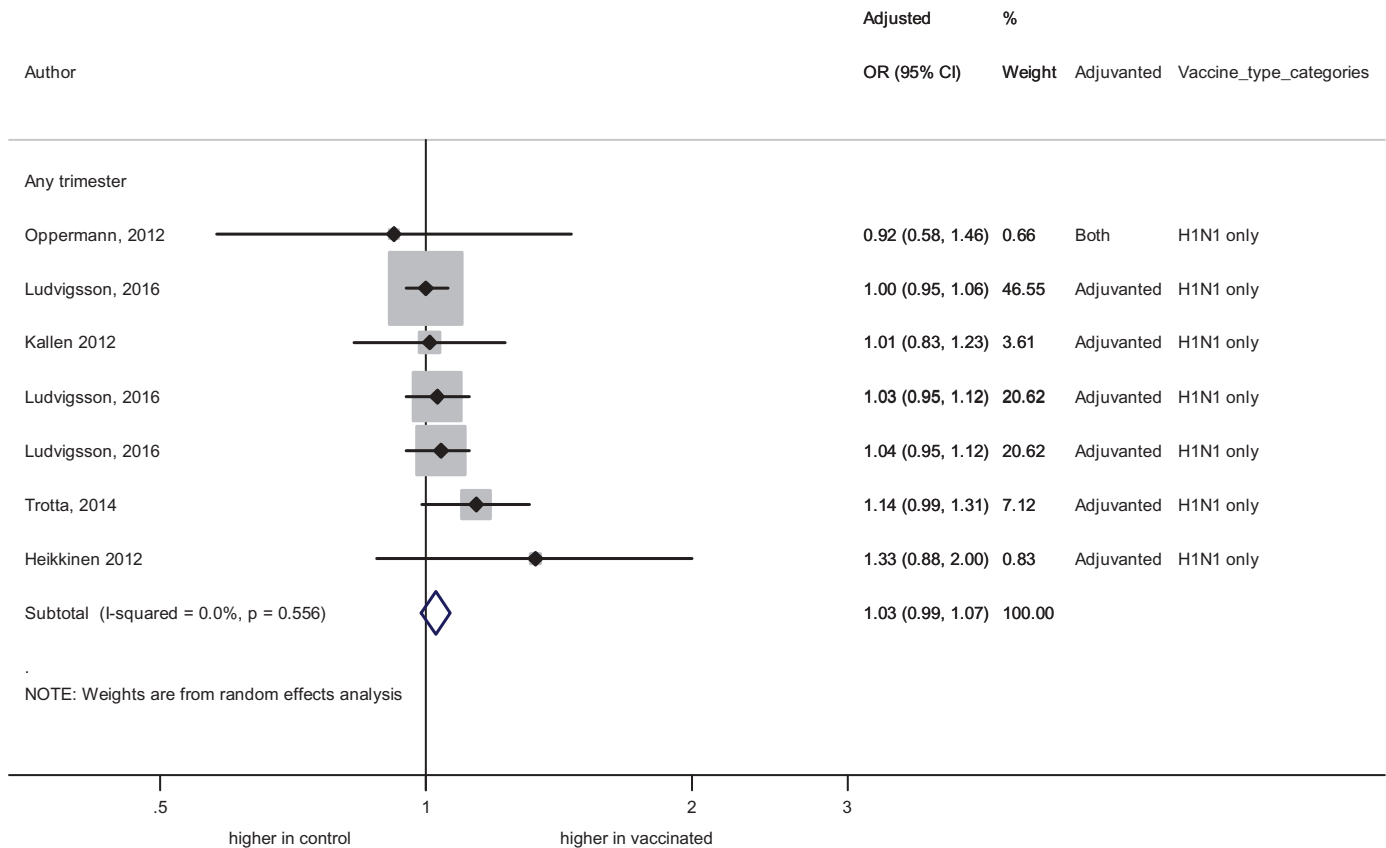


Figure 4. Congenital abnormalities.
Adjusted Odds Ratio

illness with an overall efficacy of 19% and for laboratory confirmed influenza infections in infants less than 6 months of age, immunisation had an overall efficacy of 30%. In this randomized controlled trial conducted in Nepal, which included 1847 pregnant women, maternal immunisation reduced the rate of low birth weight by 15% but did not modify the rate of small for gestational age. The number of adverse obstetric events such as miscarriage, stillbirth and congenital abnormalities was not different between the placebo and vaccinated groups. Although these studies were not included in our systematic review due to date of publication they further strengthen the safety data we report and add additional high quality evidence for benefits to the newborn against respiratory illness in the first 6 months of life.

Of all the outcomes of interest included in this systematic review, stillbirth and spontaneous abortion were the most challenging to assess, due to a lack of consistent definition and limited data. Many studies differed on the cut off gestational age that defines a stillbirth, ranging from fetal death after 20 weeks to after 28 weeks. Spontaneous abortion was not commonly included in observational studies, as reflected by the smallest number of vaccinated women included in the analysis (6471 compared to > 100,000 for all other outcomes)

and often studies did not include a definition pertaining to this term. Other factors that make this outcome challenging to assess include the timing of pregnancy and diagnostic confirmation, and non-healthcare seeking behavior.

In 2017, Donahue and colleagues reported an association of spontaneous abortion with receipt of inactivated influenza vaccine containing A/H1N1pdm2009 antigen.⁶⁷ This case-control study, conducted over two influenza seasons, reported an adjusted odds ratio of 2.0 (95% CI 1.1–3.6) for vaccine receipt within 28 days of spontaneous abortion in women who had received an influenza vaccine in the previous season in a post hoc analysis. There was no association for any other exposure window found. This is in contrast to our findings, and to other studies which have reported no increased risk.^{13,15} Similarly, a study published in 2017 of 102 spontaneous, pregnancy specific reports of adverse events following influenza vaccination submitted to the United States Vaccine Adverse Events Reporting System found no increase in spontaneous abortion.⁶⁸ Although Donahue and colleagues state that their results do not confirm causality, the findings do highlight the importance of ongoing vigilance in reporting safety of influenza vaccines in pregnancy.

Small for gestational age

Adjusted OR of outcome

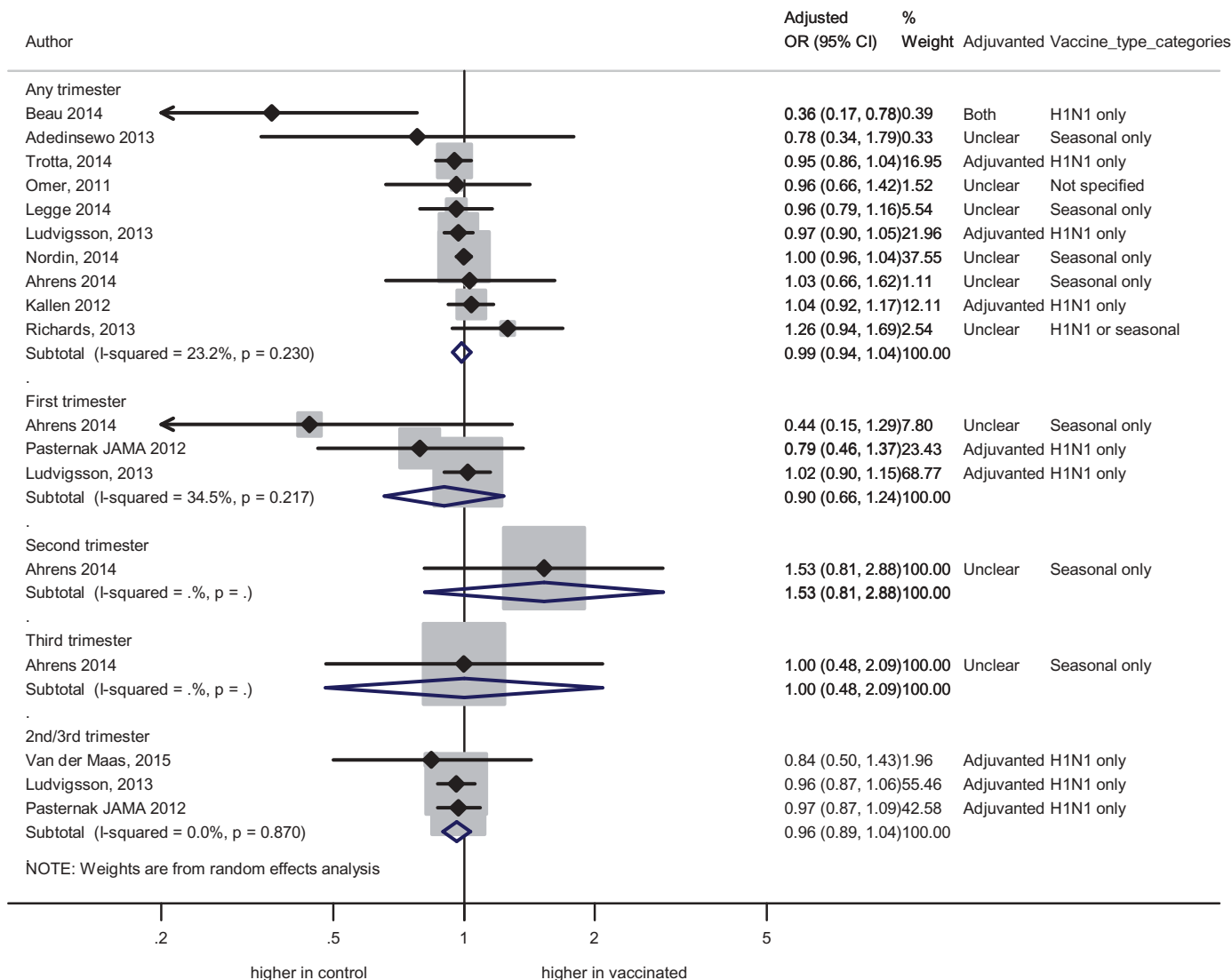


Figure 5. Small for gestational age. Adjusted Odds Ratio

As maternal immunization gains momentum as a promising intervention to reduce neonatal mortality and morbidity from a number of diseases the increased interest requires a consistent approach to monitoring safety. The Global Alignment of immunization safety assessment in pregnancy (GAIA) project was formed to improve the outcome data quality from clinical vaccine trials in pregnant women with a specific focus on safety monitoring in low and middle-income countries.¹⁸ The three main objectives of the GAIA project are to: (i) improve comparability of safety data across products, programs and populations; (ii) optimize the value of local investigations by global harmonization of methods; and (iii) increase analytic power. As part of this, development of standardised case definitions has been a priority. GAIA will be very important for future studies to adopt to facilitate easier

comparisons and meta-analyses, but has limited capacity to apply to past studies.

There are several limitations related to the findings of this systematic review. The first is that only one randomized controlled study was identified. Secondly, the majority of studies were conducted in high income settings. Although maternal influenza vaccination is not currently recommended in many low and middle income countries, it is being considered along with a number of other maternal vaccines, so the publication of safety data from these settings will be essential for the future confidence by policy makers. The underrepresentation from low and middle income countries has been identified by the WHO Working Group convened between 2014–2017 to evaluate influenza disease burden and vaccine efficacy to

Fetal death

Adjusted OR of outcome

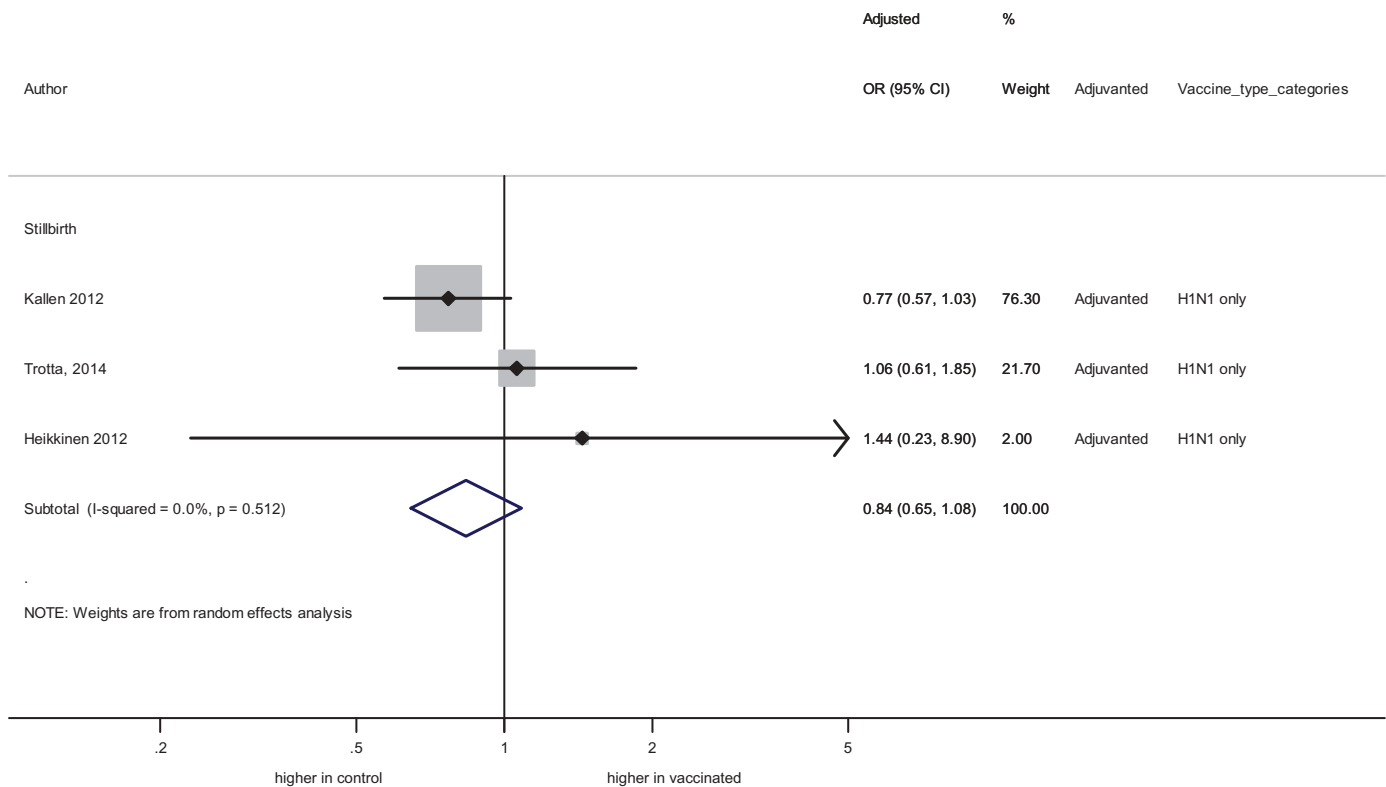


Figure 6. Fetal death (stillbirth).
Adjusted Odds Ratio

inform estimates of maternal influenza immunisation programs.⁶⁹ Of the 40 included studies in this review, only 15 contained brand specific information. In addition, only 13 specified use of adjuvanted vaccines and 6 non-adjuvanted vaccines. This means that the power to draw conclusions for individual vaccines or for adjuvanted versus non-adjuvanted is reduced. In addition, the background rate of adverse pregnancy outcomes used to calculate the number needed to vaccinate to harm is based on published data from a resource rich setting.⁷⁰ The authors acknowledge that the rate of preterm birth, congenital abnormalities, stillbirth, small for gestational age and low birth weight vary across settings and this figure may under or over represent the potential benefit/harm depending on the chosen comparator.

In addition, given influenza vaccine is recommended in all trimesters of pregnancy, there is considerable interest in outcomes according to timing of maternal vaccination. In particular, there is debate as to whether vaccination in the second and third trimesters is relevant to the outcome of congenital abnormality compared with vaccination in the first trimester. In this systematic review 24 of the 40 studies did not assess the outcome of interest according to timing of maternal vaccination. Ten studies performed the analysis by trimester, but there were still inconsistencies with three of these ten combining second and third trimesters together. As many studies do not examine the outcome according to gestation of vaccination, when this is

applied, the numbers of exposed, particularly in the first trimester are significantly reduced, thereby reducing the power to detect differences between the exposed and control group.

In addition, for outcomes such as preterm birth, most studies accounted for potential confounding by factors such as maternal age, socioeconomic status, past history of preterm birth or smoking but few studies stratified their analysis by gestational age at the time of vaccination or period of influenza activity. Given that preterm birth has been linked to a pro-inflammatory milieu which may be induced by influenza infection,⁷¹ and numerous observational studies have reported higher rates of preterm birth associated with hospitalization for respiratory illness during pregnancy,⁷² it is biologically plausible that there is a protective effect of maternal influenza vaccination on preterm birth particularly during periods of influenza circulation. Inconsistencies in different study results may be attributable to differences in baseline immunity to influenza in the study population, degree of match between vaccine and circulating strains for the season under investigation, seasonal variation in pathogenicity and study design, which could not be assessed from the available published data. In addition, some authors have highlighted the importance of considering immortal time bias when considering preterm birth.⁷³ Immortal time in cohort studies is the time period of follow up during which the study outcome of interest

cannot occur by study design. So, in studies looking for an association between influenza vaccination exposure and an outcome such as preterm birth, the immortal time is that between conception and vaccination (during which the participant is considered in the unexposed group). To account for this vaccination status can be considered a time varying variable. When this is done the results may shift from a decreased risk of preterm birth to no association.⁷³

Overall, our findings are consistent with previous reports; that there is no increased risk of adverse outcome associated with vaccination during pregnancy, and in fact may protect against some of these outcomes.

Conclusion

A large number of studies over decades investigating the safety of influenza vaccination in pregnancy, and the findings of our review, affirm that there is no evidence of an increased risk of adverse pregnancy outcomes following influenza vaccination in pregnancy. Despite this reassuring finding, there remain some important areas where more data from ongoing surveillance and formal research projects for pregnancy-related safety of vaccination would be beneficial. This includes further research on the safety of adjuvanted vaccines in pregnancy, particularly their use in first trimester, to establish a more comprehensive safety profile. In addition, future studies should aim to analyse outcomes according to consistent, reproducible definitions and according to trimester of exposure, thus allowing application of meta-analyses to harmonized aggregate data on outcome measure across multiple settings. Furthermore, interpreting the results in relation to the circulating influenza activity that season and the relative match of the vaccine with circulating virus strain would be valuable to provide greater understanding to the potential benefit (as compared to lack of increased risk) for pregnancy outcomes such as low birth weight and preterm birth.

Inclusion of national or WHO recommendations for vaccine use during pregnancy in the product information, when aligned with the product's safety profile and supported by quality evidence review, may help improve vaccine uptake in pregnancy. The results from this systematic review can be included as further evidence that the large body of evidence confirms no increased risk of adverse pregnancy outcomes, particularly for non-adjuvanted inactivated influenza vaccines. Vaccine manufacturers are encouraged to consider this body of evidence and include it when writing their product information for pregnant women.

The policy implications of this systematic review relate to translation of safety data to healthcare providers and consumers to improve uptake. This is challenging however, and needs to be considered in addition to other factors that may impact on uptake during pregnancy such as accessibility, affordability and healthcare provider recommendation.

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Contribution to Authorship

MG and SK were involved in planning and carrying out the screening of abstract and titles. They were also involved in assessing full texts for retrieval, assessing their quality, collecting the data, interpreting the analysis and writing up of the manuscript.

KM was involved in planning of the study, interpreting the analysis and writing up of the manuscript.

AC was involved in carrying out the analysis, interpreting the data and writing up of the manuscript.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Ethics Approval

Ethics approval was not required for the purpose of this systematic review

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