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RESEARCH ARTICLE

The risk of major structural birth defects associated with seasonal influenza vaccination during pregnancy: A population-based cohort study

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Abstract

Introduction: Seasonal inactivated influenza vaccine (IIV) is routinely recommended during pregnancy to protect both mothers and infants from complications following influenza infection. While previous studies have evaluated the risk of major structural birth defects in infants associated with prenatal administration of monovalent pandemic IIV, fewer studies have evaluated the risk associated with prenatal seasonal IIV.

Methods: We conducted a population-based cohort study of 125,866 singleton births between 2012 and 2016 in Western Australia. Birth registrations were linked to the state's registers for congenital anomalies and a state prenatal vaccination database. We estimated prevalence ratios (PR) of any major structural birth defect and defects by organ system. Vaccinated pregnancies were defined as those with a record of IIV in the first trimester. Inverse probability treatment weighting factored for baseline probability for vaccination. A Bonferroni correction was applied to account for multiple comparisons.

Results: About 3.9% of births had a major structural birth defect. Seasonal IIV exposure during the first trimester was not associated with diagnosis of any major structural birth defect diagnosed within 1 month of birth (PR 0.98, 95% CI: 0.77, 1.28) or within 6 years of life (PR 1.02, 95% CI: 0.78, 1.35). We identified no increased risk in specific birth defects associated with seasonal IIV.

Conclusion: Based on registry data for up to 6 years of follow-up, results suggest there is no association between maternal influenza vaccination and risk of major structural birth defects. These results support the safety of seasonal IIV administration during pregnancy.

KEYWORDS

developmental anomaly, influenza vaccine, major birth defects, maternal vaccination, pregnant women

1 | BACKGROUND

Physiologic and immunological changes during pregnancy place pregnant women at increased risk of severe influenza infection and its complications, particularly in the latter stages of pregnancy (Dodds et al., 2007). Deaths observed among pregnant women during the 2009 H1N1 influenza pandemic highlighted the potential risk of influenza to pregnant women (Pierce, Kurinczuk, Spark, Brocklehurst, & Knight, 2011). Seasonal inactivated influenza vaccine (IIV) administered during pregnancy has been shown to protect both mothers and their infants against influenza (Nunes & Madhi, 2018; Omer et al., 2020). In Australia, as with many other high-income countries, seasonal IIV is recommended during any stage of pregnancy, and has been offered universally to all women free of charge by the Australian government since 2010 (Australian Technical Advisory Group on Immunisation, 2018). Despite this, more than 40% of women in Australia do not receive a seasonal IIV during pregnancy and vaccine safety has been frequently cited as a reason for vaccine refusal (Regan et al., 2016).

Many studies on the safety of antenatal influenza vaccines have commonly examined outcomes such as preterm birth, small for gestational age, and low birthweight. Two systematic reviews encompassing 23 and 19 studies, respectively have collectively assessed the prevalence of birth outcomes following administration of pandemic influenza vaccines (Nunes, Aqil, Omer, & Madhi, 2016; Zhang, Wang, Liu, Zhang, & Sun, 2018). Fewer studies have evaluated the risk of major structural birth defects in infants following the administration of IIV (Louik et al., 2013; McMillan, Porritt, Kralik, Costi, & Marshall, 2015; Polyzos, Konstantelias, Pitsa, & Falagas, 2015; Louik et al., 2016; Kharbanda et al., 2017; Zhang et al., 2018; Peppa et al., 2020). What studies do exist have been mostly restricted to monovalent pandemic influenza vaccines (Louik et al., 2013; McMillan et al., 2015; Polyzos et al., 2015; Zhang et al., 2018), have included various definitions of birth defect outcomes, and have often relied on diagnostic codes from outpatient or inpatient health records (Louik et al., 2016; Kharbanda et al., 2017; Peppa et al., 2020). These records are less complete than a legally mandated register dedicated to the capture of congenital anomalies and may lack granularity (Mburia-Mwalili & Yang, 2014; Nembhard & Bower, 2016). Studies that have examined seasonal IIV support the safety of influenza vaccination during pregnancy and did not find an increased prevalence of major structural birth defects in vaccinated women (Sheffield et al., 2012; Chambers et al., 2016; Kharbanda et al., 2017; Peppa et al., 2020).

Our aim was to examine the association between antenatal seasonal IIV and major structural birth defects in offspring of women prenatally vaccinated, using data from a legally mandated state-based register of congenital anomalies diagnosed through 6 years of age among children in Western Australia.

2 | METHODS

2.1 | Study design and setting

We conducted an observational, population-based cohort study using probabilistically linked retrospective data collected in state-wide administrative health databases in Western Australia (WA). WA is the western-most state of Australia and has a population of 2.3 million, of which Aboriginal and Torres Strait Islander (hereafter referred to as Aboriginal) people comprise 6.4% of the population (Australian Bureau of Statistics, 2014). The winter respiratory virus season typically spans from May to September inclusive. The cohort included all registered births (live and stillbirths) in WA with a date of birth from April 1, 2012 to April 12, 2016.

2.2 | Data sources

Cohort records were probabilistically linked to the Midwives Notification System, the WA Antenatal Vaccination Database (WAAVD), and the state's register for congenital anomalies, the WA Register for Developmental Anomalies (WARDA), based on maternal information, by the Data Linkage Branch of the Department of Health Western Australia. The Midwives Notification System is a statutory data collection with information on pregnancy, labor, and birth, including maternal and infant sociodemographic and health factors, and includes information on 99% of births with gestational age ≥ 20 weeks and birthweight ≥400 g (where gestational age is unknown) in WA (Anonymous, 2021). The WAAVD is a state-wide database with collated information on vaccines administered during pregnancy between 2012 and 2016, including patient identifiers, vaccine brand, batch number, and date of vaccination (Regan et al., 2015). Information is submitted to the Department of Health Western Australia by the provider administering a vaccine to a pregnant woman. Previous validation of WAAVD has demonstrated specificity and positive predictive values exceeding 95% (Regan et al., 2015). WARDA is a legally mandated register compiling records of up to 10 major and minor birth defects per subject diagnosed in utero, at, and following birth, and up to the age of 6 years using active and passive case ascertainment to provide accurate information in a timely manner. Conditions diagnosed in utero require postnatal

confirmation by specialist review and ultrasound (Anonymous, 2015). The quality of data in WARDA has been evaluated and is estimated to be high, with only 1.5% of missing data of the 20 essential variables collected by WARDA (Nembhard & Bower, 2016).

2.3 | Exposure definition

Vaccination status was derived from the presence of a vaccination record from the WAAVD. In our primary analysis, "vaccinated" pregnancies were defined as those with a record of seasonal IIV during the first trimester (weeks 0–13 of pregnancy), similar to previous studies that have used the first trimester as the exposure period (McMillan et al., 2015; Louik et al., 2016; Kharbanda et al., 2017). Unvaccinated pregnancies were defined as women who had no record of exposure to seasonal IIV during their pregnancy. Additional analyses were conducted to consider specific periods of organogenesis for each structural birth defect category, where we defined "vaccinated" pregnancies as those with a record of IIV during the critical window of fetal organogenesis (Buck Louis, 2011).

2.4 | Outcome definitions

Our primary outcome was the presence of major structural birth defects among live and stillbirths, as recorded in WARDA prenatally and/or through to 6 years of age. We considered major structural defects in specific organ systems, based on the 5-digit British Pediatric Association extension of the International Classification of Diseases version 9 (BPA-ICD9). WARDA is an affiliate world member of EUROCAT and uses this coding to contribute data as a Member of the International Clearing House of Birth Defects Surveillance and Monitoring. Defects primarily associated with prematurity are excluded from WARDA.

2.5 | Covariates

Covariates included maternal age, Aboriginal status, socioeconomic status, parity, and maternal preexisting medical conditions (asthma, chronic hypertension, pregestational diabetes), pregnancy complications (gestational diabetes, gestational hypertension, preeclampsia), smoking status during pregnancy, and the gestational age at the time of first antenatal care visit. Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage, which is an area-based measure of relative access to resources for households within the same census collection district (Australian Bureau of Statistics). Socioeconomic status was represented as quintiles, with Quintile 1 being the most disadvantaged and Quintile 5 being the least disadvantaged. All covariates were selected a priori as known indicators of maternal influenza vaccination and healthcare seeking behavior (Yuen & Tarrant, 2014; Lutz, Carr, Cohn, & Rodriguez, 2018; Mak, Regan, Vo, & Effler, 2018). Maternal age, the presence of gestational and pregestational diabetes, and smoking during pregnancy are all known to be also associated with a higher prevalence of birth defects (Harris et al., 2017).

2.6 | Exclusions

For this analysis, we excluded plural pregnancies, births with chromosomal abnormalities, and births with congenital infections, from the cohort. As our analysis was a safety study and our hypothesis was that antenatal vaccines were safe, we have been conservative in our exclusions for this study and have opted to include congenital developmental dysplasia of the hip (DDH) in our assessment. However, given previous studies investigating the association between IIV and birth defects have excluded DDH, we considered additional analyses with DDH excluded. Finally, we excluded births with missing covariate information.

2.7 | Patient and public involvement

As this is a retrospective study of de-identified, linked data, patients cannot be involved in the design, recruitment, or conduct of the study. Consumer and community input into the project was regularly sought by the WA Healthy Pregnancies Reference Group at Curtin University. Research findings will be incorporated into communication materials for the community.

2.8 | Statistical analyses

Baseline demographic and health characteristics of the cohort were compared by vaccination status and trimester of vaccination. The unadjusted odds of vaccination compared the odds of first trimester seasonal IIV vaccination relative to unvaccinated women using univariate logistic regression models.

We estimated the prevalence ratios (PR) with 95% confidence intervals (CI) of major structural birth defect

categories, comparing first trimester vaccinated to unvaccinated pregnancies. Prevalence ratios were estimated using a generalized linear model with binomial family and log link. Robust variance estimators were calculated using sandwich estimators to account for within-mother correlation between observations (Rogers, 1994). Outcomes with less than 5 cases were suppressed. Prevalence ratios were weighted using the inverse probability treatment weighting (IPTW) to factor for baseline probability of influenza vaccination. Treatment weights were derived using multivariate logistic regression to estimate the probability of vaccination by maternal age at delivery, season and year of birth, mother's race/ethnicity, parity, smoking status, an indicator of antenatal care (first antenatal care visit in the first trimester), mother's medical conditions (asthma, chronic hypertension, and pregestational diabetes), and socioeconomic status. Stabilized weights were derived by using z-scores (Taylor, 2012). Covariate balance in the unweighted and weighted sample was confirmed based on visual inspection of the standardized differences (Figure S1). Finally, we conducted a post hoc analysis to account for multiple comparisons using a Bonferroni correction. A post hoc power analysis was also carried out (Table S1). Analyses were conducted in Stata version 15 (College Station, Texas).

2.9 | Sensitivity and quantitative bias analyses

We conducted several sensitivity analyses to evaluate whether our results were sensitive to different definitions of our cohort, exposure, and outcomes. We performed analyses to a cohort restricted to live births. To assess for possible selection bias due to the exclusion of women vaccinated in second or third trimester, we performed an analysis which classified pregnancies where vaccination occurred after the first trimester as "unvaccinated". We also performed an analysis which restricted the outcome to diagnoses of major structural birth defects made within the first month of life. This analysis is thought to more closely align with previous research relying on diagnostic coding from birth records with a similar follow-up time (Rubinstein et al., 2013; Cleary, Rice, Eogan, Metwally, & McAuliffe, 2014; Trotta et al., 2014). In other sensitivity analyses, we restricted the cohort to a single birth for each mother (Tables S5 and S6), and performed an annual analysis for any congenital malformation (Table S7), as the antigenic composition of seasonal influenza vaccines can change year to year. Finally, we performed quantitative bias analyses to consider the potential influence of exposure misclassification on study results using the episensr() package in R (Haine, 2021; Figure S4). We considered both nondifferential and differential sensitivity values for exposure measurement. Inputs into the quantitative bias analysis were derived from a previous validation study of the WAAVD (Regan et al., 2015).

3 | RESULTS

3.1 | Study characteristics

Between April 2012 and April 2016, 138,051 live and 926 stillbirths were identified among 115,439 women. We excluded 3,909 plural pregnancies from analysis. A further 274 births with a postnatal diagnosis of chromosomal anomalies and 23 births with a congenital infection (rubella, syphilis, cytomegalovirus, varicella, herpes simplex, and toxoplasma) were also excluded, as were 8,905 births with missing covariate information (Figure S2). The final cohort included 125,866 singleton births, of whom 4,864 (3.9%) were diagnosed with a major structural defect. The most frequent major structural defects were musculoskeletal defects (51.7%), followed by urogenital defects (10.4%), cardiac defects (4.1%), and central nervous system defects (2.7%) (Table S2).

The majority of central nervous system, cardiac, and urogenital system defects were diagnosed during pregnancy, in contrast to musculoskeletal defects, eye, ear, and skin defects which were diagnosed 6–12 months after birth or more than 12 months after birth (Figure S3). Over 60% of musculoskeletal defects were diagnosed after 1 month of age.

Overall, 13,696 (10.9%) births occurred in women with a record of seasonal IIV during pregnancy, 2,817 (20.6%) of whom received seasonal IIV in the first trimester, 5,650 (41.3%) received IIV in the second trimester, and 5,229 (38.2%) in the third trimester. First trimester vaccinated women were more likely to be older, primiparous, nonsmokers, have received early antenatal care, and be diabetic (Table 1).

Overall, seasonal IIV exposure during the first trimester was not associated with any major structural birth defect (weighted PR 1.02, 95% CI: 0.84, 1.24). When examined by organ system categories of major structural birth defects, seasonal IIV exposure in the first trimester was not associated with central nervous system, cardiac, or urogenital organ system defects, and was associated with musculoskeletal defects (PR 1.30, 95% CI: 1.01, 1.67; Table 2). This increased prevalence was mainly due to an increased prevalence of DDH (PR 1.37, 95% CI: 1.05, 1.79) but not for other musculoskeletal defects (PR 1.02, 95% CI: 0.51, 2.03). After adjusting for multiple comparisons using a Bonferroni correction, this association was no longer significant.

TABLE 1 Baseline characteristics of singleton pregnancies by receipt of seasonal inactivated influenza vaccine, Western Australia, April 2012–April 2016

Maternal characteristic	Unvaccinated[a] ($n = 111,125$) *n* (%)	Vaccinated during first trimester ($n = 2,811$) *n* (%)	Vaccinated during second or third trimester ($n = 10,879$) *n* (%)	Unadjusted odds ratio of vaccination in the first trimester[b] (95% CI)
Age at delivery, years				
≤19	3,547 (3.2)	66 (2.3)	388 (3.6)	0.89 (0.68, 1.16)
20–24	15,218 (13.7)	318 (11.3)	1,392 (12.8)	Referent
25–29	31,650 (28.5)	794 (28.3)	2,979 (27.4)	1.20 (1.05, 1.37)
30–34	37,661 (33.9)	1,022 (36.4)	3,853 (35.4)	1.30 (1.14, 1.47)
≥35	23,049 (20.7)	611 (21.7)	2,267 (20.8)	1.27 (1.11, 1.45)
Aboriginal or Torres Strait islander				
Aboriginal	5,791 (5.2)	144 (5.1)	600 (5.5)	0.98 (0.83, 1.16)
Nonaboriginal	105,334 (94.8)	2,667 (94.9)	10,279 (94.5)	Referent
Parity				
Primiparous	33,732 (30.4)	948 (33.7)	3,555 (32.7)	Referent
Multiparous (1 previous birth)	34,175 (30.8)	898 (32.0)	3,364 (30.9)	0.93 (0.85, 1.03)
Multiparous (>1 previous birth)	43,218 (38.9)	965 (34.3)	3,960 (36.4)	0.79 (0.73, 0.87)
Season of birth				
Summer	28,709 (25.8)	1,274 (45.3)	969 (8.9)	Referent
Autumn	30,156 (27.1)	325 (11.6)	1,583 (14.5)	0.24 (0.21, 0.27)
Winter	25,601 (23.0)	57 (2.0)	4,866 (44.7)	0.05 (0.04, 0.07)
Spring	26,659 (24.0)	1,155 (41.1)	3,461 (31.8)	0.98 (0.90, 1.06)
Month and year of birth				
2012 (April–December)	21,340 (19.2)	169 (6.0)	1,176 (10.8)	Referent
2013 (January–December)	27,729 (25.0)	729 (25.9)	2,290 (21.1)	3.32 (2.81, 3.93)
2014 (January–December)	27,824 (25.0)	765 (27.2)	2,548 (23.4)	3.47 (2.94, 4.10)
2015 (January–December)	25,870 (23.3)	776 (27.6)	4,520 (41.6)	3.79 (3.20, 4.48)
2016 (January–April)	8,362 (7.5)	372 (13.2)	345 (3.2)	5.6 (4.68, 6.75)
Preexisting medical conditions				
Essential hypertension	1,464 (1.3)	48 (1.7)	199 (1.8)	1.30 (0.97, 1.74)
Preexisting diabetes mellitus	940 (0.9)	47 (1.7)	139 (1.3)	1.99 (1.48, 2.68)
Asthma	11,481 (10.3)	313 (11.1)	1,214 (11.2)	1.09 (0.97, 1.23)
Smoking status				
Smoker	11,168 (10.0)	224 (8.0)	1,029 (9.5)	0.77 (0.68, 0.89)
Nonsmoker	99,957 (90.0)	2,587 (92.0)	9,850 (90.5)	Referent
First antenatal care visit				
First trimester	73,441 (66.1)	2,092 (74.4)	3,182 (29.3)	Referent
Second or third trimester	37,684 (33.9)	719 (25.6)	7,697 (70.8)	0.67 (0.62, 0.73)

TABLE 1 (Continued)

Maternal characteristic	Unvaccinated[a] ($n = 111,125$) n (%)	Vaccinated during first trimester ($n = 2,811$) n (%)	Vaccinated during second or third trimester ($n = 10,879$) n (%)	Unadjusted odds ratio of vaccination in the first trimester[b] (95% CI)
Socioeconomic status index (SEIFA)[c]				
Quintile 1 (most disadvantaged)	21,896 (19.7)	478 (17.0)	2,082 (19.1)	0.76 (0.67, 0.86)
Quintile 2	22,958 (20.7)	561 (20.0)	2,317 (21.3)	0.85 (0.76, 0.95)
Quintile 3	23,358 (21.0)	559 (19.9)	2,246 (20.7)	0.83 (0.74, 0.93)
Quintile 4	22,128 (19.9)	615 (21.9)	2,176 (20.0)	0.97 (0.86, 1.08)
Quintile 5 (least disadvantaged)	20,786 (18.7)	598 (21.3)	2,058 (18.9)	Referent
Any major birth defect				
Yes	4,216 (3.8)	114 (4.1)	481 (4.4)	1.07 (0.89, 1.30)
No	106,909 (96.2)	2,703 (96.0)	10,398 (95.6)	Referent

Note: Total does not add up to 125,866 as there were 1,051 women with indeterminate vaccination status.
Abbreviation: CI, confidence interval.
[a]"Unvaccinated" refers to women who had no record of vaccination with seasonal IIV during their pregnancy.
[b]Unadjusted odds of first trimester vaccination relative to unvaccinated.
[c]SEIFA stands for Socioeconomic Index for Areas, an index of relative socioeconomic advantage and disadvantage, and an area-based measure of relative access to resources for households within the same census collection district (Australian Bureau of Statistics, 2016: https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2033.0.55.001~2016~Main%20Features~SEIFA%20Basics~5).

Based on our analysis restricted to diagnoses made within 1 month of birth, we similarly observed no increase in the prevalence of any major structural birth defects (PR 0.98, 95% CI: 0.77, 1.28) or defects of specific organ systems (Table 3). When we considered critical window period of fetal organogenesis, we observed no increase in the risk of any major structural birth defects (PR 0.91, 95% CI: 0.66, 1.26) or defects of specific organ systems (Table 4). We also did not observe an increase in the prevalence of DDH (PR 1.27, 95% CI: 0.83, 1.95). Similarly, antenatal seasonal IIV vaccination in the first trimester was not associated with major birth defects in children overall when stillbirths were excluded from the cohort (PR 1.01, 95% CI: 0.83, 1.23). The prevalence of DDH was higher among liveborn infants for vaccinated births compared with unvaccinated births (PR 1.37, 95% CI: 1.05, 1.79) (Table S3). As with our primary analysis, when we accounted for multiple comparisons, this association was no longer significant. We observed no association between seasonal IIV vaccination and the prevalence of any major structural birth defects when we classed those vaccinated in second or third trimester of pregnancy as "unvaccinated" (PR 1.02, 95% CI: 0.84, 1.23) (Table S4). We also did not observe an association with DDH in these analyses (PR 1.32, 95% CI: 1.00, 1.72).

In sensitivity analyses restricted to a single birth for each mother (Tables S5 and S6), results supported our primary findings. As the antigenic composition of seasonal influenza vaccines can change by year, we performed an annual analysis for any congenital malformation. Our results did not identify differences in prevalence ratios by vaccine year (Table S7). Since our sample size of diagnosed defects was poorly powered to detect differences in specific defects by year, we did not perform annual analyses for specific types of defects.

Quantitative bias analyses indicated that given nondifferential exposure misclassification by outcome status, the corrected PR comparing the prevalence of birth defects among vaccinated versus unvaccinated pregnancies would be 1.12 (95% CI 0.82, 1.53). To change study conclusions, the sensitivity of exposure measurement would need to be 16% lower or 10% higher among those without the outcome compared with those with the outcome (Figure S4).

4 | DISCUSSION

4.1 | Main findings

Based on this cohort study of 125,866 births, our results suggest seasonal IIV administered during pregnancy is not associated with increased prevalence of major structural birth defects. One of the most common reasons that women refuse or are reluctant to receive vaccines is concerns about the safety of the vaccine for their unborn child (Omer et al., 2020). Our results support the safety of influenza vaccination during pregnancy for the development of the infant. Given vaccination rates for pregnant women remain suboptimal, these results can be used to

TABLE 2 Prevalence ratios of major structural birth defects diagnosed prenatally or within 6 years of birth by receipt of seasonal inactivated influenza vaccination during pregnancy, Western Australia, April 2012–April 2016

Birth defect	Unvaccinated[a] (*N* = 111,125)	First trimester vaccinated[a] (*N* = 2,811)			
	n (rate per 1,000 births)	*n* (rate per 1,000 births)	Unweighted PR[b] (95% CI)	Weighted PR[c] (95% CI)	Weighted PR[c] (99.5% CI)[d]
Any major defects	4,216 (37.9)	114 (40.6)	1.07 (0.89, 1.28)	1.02 (0.84, 1.24)	1.02 (0.78, 1.35)
Central nervous system defects	302 (2.7)	5 (1.8)	0.65 (0.27, 1.58)	0.62 (0.24, 1.57)	0.62 (0.16, 2.36)
Cardiac system defects	440 (4.0)	11 (3.9)	0.99 (0.54, 1.79)	0.80 (0.44, 1.47)	0.80 (0.34, 1.91)
Musculoskeletal system defects	2,129 (19.2)	72 (25.6)	1.34 (1.06, 1.69)	1.30 (1.01, 1.67)	1.30 (0.91, 1.86)
Hip dysplasia	1,709 (15.2)	63 (22.4)	1.45 (1.13, 1.88)	1.37 (1.05, 1.79)	1.37 (0.94, 2.01)
All other musculoskeletal defects	420 (3.7)	9 (3.2)	0.85 (0.44, 1.64)	1.02 (0.51, 2.03)	1.02 (0.38, 2.73)
Eye defects	35 (0.3)	0 (0)	–[e]	–[e]	–[e]
Ear, face, head, or neck defects	24 (0.2)	<5	–[e]	–[e]	–[e]
Urogenital system defects	1,177 (10.6)	26 (9.2)	0.87 (0.59, 1.28)	0.80 (0.53, 1.20)	0.80 (0.45, 1.43)
Defects of the ureter/bladder	303 (2.7)	6 (2.1)	0.78 (0.35, 1.75)	0.72 (0.31, 1.69)	0.72 (0.21, 2.44)
Hydronephrosis	369 (3.3)	11 (3.9)	1.17 (0.65, 2.14)	1.01 (0.55, 1.89)	1.01 (0.42, 2.47)
Gastrointestinal system defects	274 (2.5)	<5	–[e]	–[e]	–[e]
Integumentary system defects	22 (0.2)	<5	–[e]	–[e]	–[e]
Respiratory system defects	81 (0.7)	<5	–[e]	–[e]	–[e]
Other defects or conditions	152 (1.4)	<5	–[e]	–[e]	–[e]

Abbreviations: CI, confidence interval; PR, prevalence ratio.

[a]Vaccinated in the first trimester, defined as weeks 0–13 of gestation for the analysis; Unvaccinated defined as women who had no record of IIV during their pregnancy.

[b]Prevalence ratios and corresponding 95% confidence intervals were calculated using a generalized linear model with binomial family and log link.

[c]Weighted prevalence ratios were weighted by the inverse probability of treatment weight based on the estimated probability for vaccination. Treatment weights accounted for the probability of vaccination by maternal age, mother's ethnicity, parity, season of birth, smoking status, sex, antenatal care indicator, mother's medical conditions, and disadvantage.

[d]99.5% confidence intervals reflect a Bonferroni correction for multiple comparisons.

[e]Estimates were not calculated due to small cell size ($n < 5$).

support vaccine decision-making for pregnant women and their healthcare providers.

4.2 | Interpretation

These results are in keeping with other studies that have examined the safety profile of influenza vaccination during pregnancy which have consistently shown no association between seasonal or pandemic IIV vaccination and the prevalence of major birth defects in offspring of mothers vaccinated during the antenatal period (Polyzos et al., 2015; Louik et al., 2016; Kharbanda et al., 2017; Peppa et al., 2020). Previous studies have provided similar estimates to ours, with prevalence ratios that range from 0.5 to 1.5 and prevalence odds ratios that ranged from 0.6 to 2.2, and imprecise confidence intervals that crossed the null value (Polyzos et al., 2015; Louik et al., 2016; Kharbanda et al., 2017; Peppa et al., 2020).

TABLE 3 Prevalence ratios of major structural birth defects diagnosed prenatally or within 1 month of birth by receipt of seasonal inactivated influenza vaccination during pregnancy, Western Australia, April 2012–April 2016

Birth defect	Unvaccinated[a] ($N = 112,125$)	First trimester vaccinated[a] ($N = 2,811$)			
	n (rate per 1,000 births)	*n* (rate per 1,000 births)	Unweighted PR[b] (95% CI)	Weighted PR[c] (95% CI)	Weighted PR[c] (99.5% CI)[d]
Any major defects	2,491 (22.4)	62 (22.1)	0.98 (0.77, 1.26)	0.98 (0.77, 1.28)	0.98 (0.68, 1.43)
Central nervous system defects	220 (2.0)	<5	–[e]	–[e]	–[e]
Cardiac system defects	350 (3.1)	9 (3.2)	1.02 (0.52, 1.96)	0.82 (0.42, 1.59)	0.82 (0.31, 2.12)
Musculoskeletal system defects	888 (7.9)	28 (10.0)	1.25 (0.86, 1.81)	1.30 (0.88, 1.92)	1.30 (0.74, 2.28)
Hip dysplasia	513 (4.6)	20 (7.1)	1.54 (0.99, 2.41)	1.53 (0.96, 2.45)	1.53 (0.79, 2.99)
All other musculoskeletal defects	375 (3.4)	8 (2.8)	0.84 (0.42, 1.70)	0.98 (0.47, 2.03)	0.98 (0.34, 2.78)
Eye defects	30 (0.3)	0 (0)	–[e]	–[e]	–[e]
Ear, face, head, or neck defects	21 (0.2)	<5	–[e]	–[e]	–[e]
Urogenital system defects	961 (8.6)	23 (8.2)	0.95 (0.63, 1.43)	0.88 (0.57, 1.37)	0.88 (0.48, 1.64)
Defects of the ureter/bladder	246 (2.2)	5 (1.8)	0.80 (0.33, 1.95)	0.77 (0.30, 1.95)	0.77 (0.20, 2.92)
Hydronephrosis	357 (3.2)	10 (3.6)	1.11 (0.59, 2.07)	0.96 (0.50, 1.85)	0.96 (0.38, 2.46)
Gastrointestinal system defects	201 (1.8)	<5	–[e]	–[e]	–[e]
Integumentary system defects	18 (0.2)	0 (0)	–[e]	–[e]	–[e]
Respiratory system defects	75 (0.7)	<5	–[e]	–[e]	–[e]
Other defects or conditions	127 (1.2)	<5	–[e]	–[e]	–[e]

Abbreviations: CI, confidence interval; PR, prevalence ratio.

[a]Vaccinated in the first trimester, defined as weeks 0–13 of gestation for the analysis; Unvaccinated defined as women who had no record of IIV during their pregnancy.

[b]Prevalence ratios and corresponding 95% confidence intervals were calculated using a generalized linear model with binomial family and log link;

[c]Weighted prevalence ratios were weighted by the inverse probability of treatment weight based on the estimated probability for vaccination. Treatment weights accounted for the probability of vaccination by maternal age, mother's ethnicity, parity, season of birth, smoking status, sex, antenatal care indicator, mother's medical conditions, and disadvantage;

[d]99.5% confidence intervals reflect a Bonferroni correction for multiple comparisons;

[e]Estimates not calculated due to small cell size ($n < 5$).

Although we observed no association between seasonal influenza vaccination and major structural birth defects overall, when we considered specific defects, we did, however, observe a slightly elevated prevalence of musculoskeletal defects among children of women vaccinated in the first trimester. The majority of these major birth defects were unilateral or bilateral DDH. Developmental hip dysplasia refers to a range of developmental hip disorders and is a common congenital deformation (Dezateux & Rosendahl, 2007), particularly in first pregnancies, large babies, and breech presentations, all factors which reduce the amount of space in the womb (Dezateux & Rosendahl, 2007). In Western Australia, diagnoses of DDH are increasingly made on the basis of ultrasound imaging and have been increasing in recent years—the reasons for which are at present unknown (Anonymous, 2015). A recent review concluded there was insufficient evidence to support universal screening,

TABLE 4 Prevalence ratios of major structural birth defects diagnosed prenatally or within 6 years of birth by receipt of inactivated influenza vaccine during the critical window of fetal organogenesis, Western Australia, April 2012–April 2016

Birth defect	Window (weeks)[a]	Unvaccinated[b] ($N = 112,125$) *n* (rate per 1,000 births)	Critical window vaccinated[b] ($N = 2,811$) *n* (rate per 1,000 births)	Unweighted PR[c] (95% CI)	Weighted PR[d] (95% CI)	Weighted PR[d] (99.5% CI)[e]
Any major defects	13	4,828 (38.7)	36 (35.2)	0.91 (0.66, 1.26)	0.91 (0.66, 1.26)	0.91 (0.58, 1.45)
Central nervous system defects	16	329 (2.7)	9 (2.3)	0.84 (0.43, 1.62)	0.98 (0.47, 2.04)	0.98 (0.34, 2.80)
Cardiac systems	6	508 (4.1)	<5	–[f]	–[f]	–[f]
Musculoskeletal systems	7	2,491 (20.0)	24 (23.5)	1.18 (0.79, 1.75)	1.18 (0.79, 1.76)	1.18 (0.67, 2.08)
Hip dysplasia	7	2,023 (16.2)	21 (20.5)	1.27 (0.83, 1.94)	1.27 (0.83, 1.95)	1.27 (0.69, 2.34)
All other musculoskeletal defects	7	468 (3.7)	<5	–[f]	–[f]	–[f]
Eye defects	8	39 (0.3)	0 (0)	–[f]	–[f]	–[f]
Ear, face, head, or neck defects	9	28 (0.2)	<5	–[f]	–[f]	–[f]
Urogenital system defects	9	1,306 (10.5)	9 (5.9)	0.56 (0.29, 1.08)	0.57 (0.30, 1.10)	0.57 (0.22, 1.46)
Defects of the ureter/bladder	9	303 (2.7)	<5	–[f]	–[f]	–[f]
Hydronephrosis	9	369 (3.3)	<5	–[f]	–[f]	–[f]
Gastrointestinal system defects	7	306 (2.5)	0 (0)	–[f]	–[f]	–[f]
Integumentary system defects	7	24 (0.2)	<5	–[f]	–[f]	–[f]
Respiratory system defects	7	89 (0.7)	<5	–[f]	–[f]	–[f]
Other defects or conditions	7	165 (1.3)	0 (0)	–[f]	–[f]	–[f]

Abbreviations: CI: confidence interval; PR: prevalence ratio.

[a]Based on critical windows outlined in Reproductive and Perinatal Epidemiology, Buck Louis, 2011.

[b]Vaccination in the first trimester, defined as weeks 0–13 of gestation for the analysis; Unvaccinated defined as women who had no record of IIV during their pregnancy.

[c]Prevalence ratios and corresponding 95% confidence intervals were calculated using a generalized linear model with binomial family and log link.

[d]Weighted prevalence ratios were weighted by the inverse probability of treatment weight based on the estimated probability for vaccination. Treatment weights accounted for the probability of vaccination by maternal age, mother's ethnicity, parity, season of birth, smoking status, sex, antenatal care indicator, mother's medical conditions, and disadvantage.

[e]99.5% confidence intervals reflect a Bonferroni correction for multiple comparisons;

[f]Estimates not calculated due to small cell sizes ($n < 5$).

that strong evidence on the diagnosis of DDH was limited and that ultrasound interpretation was prone to inter- and intra-observer variability depending especially on operator skill (Schaeffer, 2018). WARDA only ascertains cases of DDH that have been followed up and confirmed postnatally and that have required treatment with bracing. It is worth mentioning that when we accounted for multiple comparisons, the association between DDH and maternal seasonal IIV vaccination was no longer statistically significant. Furthermore, when we considered only vaccination during the critical window of development for the musculoskeletal system, we did not identify an association between vaccination and DDH. We also assessed musculoskeletal malformations with and without DDH, and both DDH and other musculoskeletal malformations in the second and third trimester. When

restricted to a single birth for each mother, we no longer see an association between vaccination and DDH. For these reasons, we think that DDH ascertained by WARDA is unlikely to be influenced by maternal vaccination status. Previous studies examining the risk of major structural birth defects after maternal seasonal IIV vaccination where DDH has been specifically mentioned have not identified an association between DDH and maternal vaccination (Kharbanda et al., 2017; Peppa et al., 2020). However, given 60% of musculoskeletal defects were diagnosed after 1 month of age in our study, it is likely that our study with the longer follow-up captured more musculoskeletal defects. As a result, although there is no strong evidence to support an association between DDH and maternal vaccination, further research would be useful.

4.3 | Strengths and limitations

A major strength of our study is that major birth defects were identified as recorded by a state-wide legally mandated register, rather than using ICD coding system algorithms to identify defects (Louik et al., 2016; Kharbanda et al., 2017; Peppa et al., 2020). The WARDA register identifies children with major and minor birth defects using both passive and active case ascertainment through a legally mandated process, in multiple data sources, including birth, death, hospitalization, and perinatal data, antenatal ultrasonography, medical records, fetal medicine departments, cytogenetic laboratories, specialty clinics, the state newborn screening laboratory, and pediatric surgery and pathology departments, and is thus more comprehensive in capturing all possible birth defect cases up to the age of 6 years (Nembhard & Bower, 2016). The register was evaluated in 2016 using the 2001 Guidelines for the evaluation of public health surveillance systems (Anonymous, 2001), as well as the "Standards for Birth Defects Surveillance" provided by the National Birth Defects Prevention Network in the United States as a framework (Anderka et al., 2015), and was found to be of high quality and representative (Nembhard & Bower, 2016). Prevalence rates from WARDA were relatively comparable to the two other surveillance systems, which indicates that the sensitivity of WARDA is fairly similar to other active surveillance systems with extended case ascertainment periods (Nembhard & Bower, 2016).

Another strength of our study is the use of a population-based cohort, including stillbirths, which would have minimized the influence of selection bias (i.e., live birth bias). Prior research has mostly been restricted to evaluation of major birth defects in cohorts of live births (Polyzos et al., 2015; Louik et al., 2016; Kharbanda et al., 2017; Peppa et al., 2020). Studies that assess exposure effects on the risk of congenital anomalies when restricted to live births only are prone to selection bias, termed "livebirth bias" (Khoshnood, 2020). Finally, to control for the possible influence of health-seeking behavior, our analytical approach accounted for the propensity for vaccination, including covariates known to influence health-seeking behavior (vaccination) in pregnant women (Lutz et al., 2018; Mak et al., 2018).

Despite these strengths, our study has some limitations. First, we did not have information on the use of teratogenic medications or hazardous alcohol consumption during pregnancy. Similarly, we did not have information on folic acid and prenatal vitamin use. While we did not identify children with fetal alcohol spectrum disorder (FASD) in our cohort, we acknowledge that FASD is likely to be under-recognized and under-reported (Burns, Breen, Bower, O'Leary, & Elliott, 2013). We did not have information on pregnancy loss prior to 20 weeks and although medical terminations at ≥20 weeks were included in the dataset, we did not have the ability to identify these losses. We were also limited by small numbers for some categories of major birth defects, such as eye, ear, gastrointestinal, respiratory, skin structural birth defect categories, and defects of the peripheral circulatory system by vaccination status, as well as specific major birth defects. Since defects of the same organ system can have different etiologies, additional research with larger cohorts with sufficient power to examine specific defects is still needed. Third, although we believe outcome misclassification would be uncommon, given the high validity of our source of birth defect information, we cannot exclude the possibility of exposure misclassification in our analysis. Based on a prior validation study of the WAAVD database, conducted at the inception of the database and reflecting worst-case scenario, the specificity and sensitivity values of the WAAVD for measuring influenza vaccination during pregnancy was 99% and 46%, respectively (Regan et al., 2015). This indicates that while misclassification of unvaccinated women as vaccinated was uncommon, but some vaccinated women may have been misclassified as unvaccinated. Based on our quantitative analysis, nondifferential exposure misclassification by outcome group would not have changed our study findings and large differences in the validity of exposure measurement by outcome group would be needed to suggest a harmful or protective association between vaccination and the prevalence of birth defects. Finally, because this is an observational study, we cannot entirely exclude the possible influence of residual confounding on our results—despite our application of

propensity score analyses to balance the cohort of vaccinated and unvaccinated pregnant individuals and to restrict the influence of confounding.

5 | CONCLUSIONS

The findings from this large cohort study, in which diagnoses in children up to the age of 6 years were included, are consistent with the results from other studies on the safety of maternal influenza vaccination and support the safety of current recommendations for influenza vaccination during pregnancy. Targeted efforts are needed to improve influenza vaccination rates among pregnant women, and such efforts will need to incorporate information on the safety of vaccination for offspring. Findings from this study are valuable in supporting vaccine confidence and can be used by healthcare providers and vaccination campaigns when communicating about the importance and safety of recommended vaccinations for pregnant women.

AUTHOR CONTRIBUTIONS

Mohinder Sarna, Gavin F. Pereira, and Annette K. Regan conceptualized, designed, and coordinated the study. Mohinder Sarna wrote the first draft. Mohinder Sarna, Damien Foo, Gavin F. Pereira, and Annette K. Regan contributed to data analysis. All authors advised on interpretation of results and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Department of Health Western Australia. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of Department of Health Western Australia.

ETHICS STATEMENT

Ethical approval was provided by the Department of Health Western Australia Human Research Ethics Committee (HREC 2016/56) on 21st October 2016, the Western Australian Aboriginal Health Ethics Committee (HREC 889) on 21st November 2018, and Curtin University Human Research Ethics Committee (HRE2017-0808) on 20th November 2017.

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REFERENCES

Anderka, M., Mai, C. T., Romitti, P. A., Copeland, G., Isenburg, J., Feldkamp, M. L., ... Kirby, R. S. (2015). Development and implementation of the first national data quality standards for population-based birth defects surveillance programs in the United States. *BMC Public Health*, *15*, 925. https://doi.org/10.1186/s12889-015-2223-2

Anonymous. (2001). Updated guidelines for evaluating public health surveillance systems. *Morbidity and Mortality Weekly Report*, *50*(RR-13), 1–35. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm

Anonymous. (2015) The West Australian Register of Developmental Anomalies. Western Australian register of developmental anomalies: 1980-2014, Department of Health, Western Australia. Retrieved from https://www.kemh.health.wa.gov.au/Our-services/WARDA.

Anonymous, 2021. The Midwives Notification System. Retrieved from https://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System.

Australian Bureau of Statistics. (2014) 1306.5 - Western Australia at a glance, 2014. Retrieved from https://www.abs.gov.au/ausstats/abs@.nsf/mf/1306.5.

Australian Bureau of Statistics, 2016. 2033.0.55.001—Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2016. Retrieved from https://www.abs.gov.

au/ausstats/abs@.nsf/Lookup/by%20Subject/2033.0.55.001~2016~Main%20Features~SEIFA%20Basics~5.

Australian Technical Advisory Group on Immunisation. (2018). The Australian Immunisation Handbook. 10th ed. Retrieved from https://immunisationhandbook.health.gov.au/.

Buck Louis, G. M. (2011). In G. M. B. Louis & R. W. Platt (Eds.), *Sensitive windows of human reproduction and development. Reproductive and perinatal epidemiology*. New York: Oxford University Press.

Burns, L., Breen, C., Bower, C., O'Leary, C., & Elliott, E. J. (2013). Counting fetal alcohol spectrum disorder in Australia: The evidence and the challenges. *Drug and Alcohol Review*, *32*, 461–467. https://doi.org/10.1111/dar.12047

Chambers, C. D., Johnson, D. L., Xu, R., Luo, Y. J., Louik, C., Mitchell, A. A., ... Jones, K. L. (2016). Safety of the 2010-11, 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS. *Vaccine*, *34*, 4443–4449. https://doi.org/10.1016/j.vaccine.2016.06.054

Cleary, B. J., Rice, U., Eogan, M., Metwally, N., & McAuliffe, F. (2014). 2009 a/H1N1 influenza vaccination in pregnancy: Uptake and pregnancy outcomes - a historical cohort study. *European Journal of Obstetrics, Gynecology and Reproductive Biology.*, *178*, 163–168. https://doi.org/10.1016/j.ejogrb.2014.04.015

Dezateux, C., & Rosendahl, K. (2007). Developmental dysplasia of the hip. *Lancet*, *369*, 1541–1552. https://doi.org/10.1016/s0140-6736(07)60710-7

Dodds, L., McNeil, S. A., Fell, D. B., AllenVM, C. A., Scott, J., & MacDonald, N. (2007). Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *Canadian Medical Association Journal*, *176*, 463–468. https://doi.org/10.1503/cmaj.061435

Haine, D. (2021) Quantitative bias analysis for epidemiologic data. https://cran.r-project.org/web/packages/episensr/vignettes/episensr.html

Harris, B. S., Bishop, K. C., Kemeny, H. C., Walker, J. S., Rhee, E., & Kuller, J. A. (2017). Risk factors for birth defects. *Obstetric and Gynecological Surveillance.*, *72*, 123–135. https://doi.org/10.1097/OGX.0000000000000405

Kharbanda, E. O., Vazquez-Benitez, G., Romitti, P. A., Naleway, A. L., CheethamTC, L. H. S., Klein, N. P., ... Nordin, J. D. (2017). First trimester influenza vaccination and risks for major structural birth defects in offspring. *The Journal of Pediatrics*, *187*, 234–239. https://doi.org/10.1016/j.jpeds.2017.04.039

Khoshnood, B. (2020). Selection bias in studies of birth defects among livebirths: Much ado about nothing? *Paediatrics and Perinatal Epidemiology.*, *34*, 665–667. https://doi.org/10.1111/ppe.12720

Louik, C., Ahrens, K., Kerr, S., Pyo, J., Chambers, C., Jones, K. L., ... Mitchell, A. A. (2013). Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: Exposure prevalence, preterm delivery, and specific birth defects. *Vaccine*, *31*, 5033–5040. https://doi.org/10.1016/j.vaccine.2013.08.096

Louik, C., Kerr, S., Van Bennekom, C. M., Chambers, C., Jones, K. L., Schatz, M., & Mitchell, A. A. (2016). Safety of the 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: Preterm delivery and specific malformations, a study from the case-control arm of VAMPSS. *Vaccine*, *34*, 4450–4459. https://doi.org/10.1016/j.vaccine.2016.06.078

Lutz, C. S., Carr, W., Cohn, A., & Rodriguez, L. (2018). Understanding barriers and predictors of maternal immunization: Identifying gaps through an exploratory literature review. *Vaccine*, *36*, 7445–7455. https://doi.org/10.1016/j.vaccine.2018.10.046

Mak, D. B., Regan, A. K., Vo, D. T., & Effler, P. V. (2018). Antenatal influenza and pertussis vaccination in Western Australia: A cross-sectional survey of vaccine uptake and influencing factors. *BMC Pregnancy and Childbirth*, *18*, 416–425. https://doi.org/10.1186/s12884-018-2051-3

Mburia-Mwalili, A., & Yang, W. (2014). Birth defects surveillance in the United States: Challenges and implications of international classification of diseases tenth revision, clinical modification implementation. *International Scholarly Research Notices*, *2014*, 212874. https://doi.org/10.1155/2014/212874

McMillan, M., Porritt, K., Kralik, D., Costi, L., & Marshall, H. (2015). Influenza vaccination during pregnancy: A systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. *Vaccine*, *33*, 2108–2117. https://doi.org/10.1016/j.vaccine.2015.02.068

Nembhard, W. N., & Bower, C. (2016). Evaluation of the Western Australian register of developmental anomalies: Thirty-five years of surveillance. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *106*, 894–904. https://doi.org/10.1002/bdra.23575

Nunes, M. C., Aqil, A. R., Omer, S. B., & Madhi, S. A. (2016). The effects of influenza vaccination during pregnancy on birth outcomes: A systematic review and meta-analysis. *American Journal of Perinatology*, *33*, 1104–1114. https://doi.org/10.1055/s-0036-1586101

Nunes, M. C., & Madhi, S. A. (2018). Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: A systematic review and meta-analysis. *Human Vaccines and Immunotherapeutics.*, *14*, 758–766. https://doi.org/10.1080/21645515.2017.1345385

Omer, S. B., Clark, D. R., Madhi, S. A., Tapia, M. D., Nunes, M. C., Cutland, C. L., ... Wairagkar, N. (2020). Efficacy, duration of protection, birth outcomes, and infant growth associated with influenza vaccination in pregnancy: A pooled analysis of three randomised controlled trials. *Lancet Respiratory Medicine*, *8*, 597–608. https://doi.org/10.1016/s2213-2600(19)30479-5

Peppa, M., Thomas, S. L., Minassian, C., Walker, J. L., McDonald, H. I., Andrews, N. J., ... Mangtani, P. (2020). Seasonal influenza vaccination during pregnancy and the risk of major congenital malformations in live-born infants: A 2010-2016 historical cohort study. *Clinical Infectious Diseases*, *73*(11), e4296–e4304. https://doi.org/10.1093/cid/ciaa845

Pierce, M., Kurinczuk, J. J., Spark, P., Brocklehurst, P., & Knight, M. (2011). Perinatal outcomes after maternal 2009/H1N1 infection: National cohort study. *British Medical Journal*, *342*, d3214. https://doi.org/10.1136/bmj.d3214

Polyzos, K. A., Konstantelias, A. A., Pitsa, C. E., & Falagas, M. E. (2015). Maternal influenza vaccination and risk for congenital malformations: A systematic review and meta-analysis. *Obstetrics and Gynecology*, *126*, 1075–1084. https://doi.org/10.1097/aog.0000000000001068

Regan, A. K., Mak, D. B., Hauck, Y. L., Gibbs, R., Tracey, L., & Effler, P. V. (2016). Trends in seasonal influenza vaccine uptake during pregnancy in Western Australia: Implications for

midwives. *Women and Birth*, *29*, 423–429. https://doi.org/10.1016/j.wombi.2016.01.009

Regan, A. K., Mak, D. B., Moore, H. C., Tracey, L., Saker, R., Jones, C., & Effler, P. V. (2015). Surveillance of antenatal influenza vaccination: Validity of current systems and recommendations for improvement. *BMC Public Health*, *15*, 1155–1162. https://doi.org/10.1186/s12889-015-2234-z

Rogers, W. H. (1994). Regression standard errors in clustered samples. *Stata Technical Bulletin*, *3*, 19–23. Retrieved from. https://www.stata-press.com/journals/stbcontents/stb13.pdf

Rubinstein, F., Micone, P., Bonotti, A., Wainer, V., Schwarcz, A., Augustovski, F., … Karolinski, A. (2013). Influenza a/H1N1 MF59 adjuvanted vaccine in pregnant women and adverse perinatal outcomes: Multicentre study. *British Medical Journal*, *346*, f393. https://doi.org/10.1136/bmj.f393

Schaeffer, E. K., I Study Group, & Mulpuri, K. (2018). Developmental dysplasia of the hip: Addressing evidence gaps with a multicentre prospective international study. *Medical Journal of Australia*, *208*, 359–364.

Sheffield, J. S., Greer, L. G., Rogers, V. L., Roberts, S. W., Lytle, H., McIntire, D. D., & Wendel, G. D., Jr. (2012). Effect of influenza vaccination in the first trimester of pregnancy. *Obstetrics and Gynecology*, *120*, 532–537. https://doi.org/10.5694/mja18.00154

Taylor, S. E. (2012). In S. Boslaugh (Ed.), *Z score. Encyclopedia of epidemiology*. Thousand Oaks: SAGE Publications, Inc.. https://doi.org/10.4135/9781412953948

Trotta, F., Da Cas, R., Spila Alegiani, S., Gramegna, M., Venegoni, M., Zocchetti, C., & Traversa, G. (2014). Evaluation of safety of a/H1N1 pandemic vaccination during pregnancy: Cohort study. *British Medical Journal*, *348*, g3361. https://doi.org/10.1136/bmj.g3361

Yuen, C. Y., & Tarrant, M. (2014). Determinants of uptake of influenza vaccination among pregnant women - a systematic review. *Vaccine*, *32*, 4602–4613. https://doi.org/10.1016/j.vaccine.2014.06.067

Zhang, C., Wang, X., Liu, D., Zhang, L., & Sun, X. (2018). A systematic review and meta-analysis of fetal outcomes following the administration of influenza a/H1N1 vaccination during pregnancy. *International Journal of Gynaecology and Obstetrics*, *141*, 141–150. https://doi.org/10.1002/ijgo.12394

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