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Seasonal Trivalent Influenza Vaccination During Pregnancy and the Incidence of Stillbirth: Population-Based Retrospective Cohort Study

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Background. Although antenatal influenza vaccination is an important public health intervention for preventing serious infection in pregnant women and newborns, reported vaccine coverage is often <50%. Concern for the safety to the fetus is a commonly cited reason for vaccine hesitancy and refusal. The incidence of stillbirth following pandemic vaccination has been previously studied; however, no population-based study has evaluated the incidence of stillbirth following seasonal trivalent influenza vaccination.

Methods. We used probabilistic linking of perinatal and maternal vaccination records to establish a cohort of 58 008 births occurring between April 2012 and December 2013. Stillbirth was defined as birth ≥20 weeks' gestation with an Apgar score of zero at 1 and 5 minutes following delivery. Cox regression models adjusted for maternal smoking, Indigenous status, and propensity for vaccination were used to calculate adjusted hazard ratios (aHRs) in vaccinated and unvaccinated mothers.

Results. A total of 5076 (8.8%) pregnant women received trivalent influenza vaccine and 377 stillbirths occurred. There were 5.0 and 3.0 stillbirths per 100 000 pregnancy-days among unvaccinated and vaccinated women, respectively. After adjustment, stillbirth was 51% less likely among vaccinated vs unvaccinated mothers (aHR, 0.49; 95% confidence interval [CI], .29–.84). The largest relative reduction in stillbirths was observed for births occurring just after influenza season (aHR, 0.33; 95% CI, .12–.88).

Conclusions. Mothers who received seasonal TIV during pregnancy were significantly less likely to experience stillbirth compared with unvaccinated mothers. These results support the safety of seasonal influenza immunization during pregnancy and suggest a protective effect.

Keywords. stillbirth; seasonal trivalent influenza vaccine; perinatal mortality; maternal immunization.

Pregnant women are at increased risk of serious complications following influenza infection, including pneumonia and acute respiratory distress syndrome [1–3]. This increased risk is thought to be the result of depressed cell-mediated immunity and physiological changes to the cardiopulmonary system associated with pregnancy [1, 3]. Influenza infection during pregnancy has also been linked to adverse fetal and neonatal outcomes, including increased risk of preterm birth [1, 4, 5] and fetal mortality; this effect has been most pronounced during influenza pandemics [1, 6]. During the recent 2009 influenza A(H1N1) pandemic, a significant increase in perinatal mortality was observed following maternal infection, most of this attributable to a 4-fold increase in stillbirths [6, 7].

Seasonal influenza vaccination has been shown to prevent infection in mothers and their newborn infants [8, 9], and the World Health Organization has indicated that pregnant women should receive the highest priority for seasonal influenza vaccination [10]. Reported vaccine uptake remains <50% in pregnant women, and concern regarding the safety of the vaccine for the fetus is a commonly cited reason why women refuse vaccination [11, 12]. Enhanced data collection and surveillance during the 2009 H1N1 pandemic offered the unique opportunity to monitor the safety of pandemic influenza vaccination in large, observational studies [13]. These studies suggested stillbirth was less common in women who received pandemic vaccine compared with unvaccinated women, supporting the safety of pandemic influenza vaccination during pregnancy [6, 13–16]; however, to date, no population-based study has been conducted to evaluate the impact of antenatal administration of seasonal influenza vaccination on stillbirth during nonpandemic influenza seasons [13, 16]. The aim of this study was to assess the relative risk of stillbirth among vaccinated and unvaccinated pregnant women during the 2012 and 2013 seasonal influenza epidemics in the winter months of the southern hemisphere.

METHODS

Western Australia has a population of 2.4 million people, with 71% residing in the Perth metropolitan area. There are

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approximately 30 000 births each year. For this analysis, multiple statewide data sources were linked by the Western Australian Data Linkage Branch of the Western Australia Department of Health, using probabilistic matching of the full name and date of birth of mothers who delivered in Western Australia between 1 April 2012 and 31 December 2013. The project was approved by the Western Australia Department of Health Human Research Ethics Committee.

Data Sources

Vaccination Status

Seasonal trivalent influenza vaccine (TIV) has been provided at no cost under the National Immunisation Program to pregnant women since 2009 and has been part of routine antenatal care in Western Australia since 2012. Postpartum surveys estimate that 25%–36% of women who were pregnant during the study period received seasonal TIV [17]. The majority of pregnant women in Australia receive their influenza vaccine from general practitioners; an additional 19% are immunized at public hospital antenatal clinics [17]. As part of ongoing vaccine safety surveillance, providers administering influenza vaccine during pregnancy under the National Immunisation Program are asked to inform the Western Australia Department of Health of the name, date of birth, and vaccination date of the expectant mother. This information is stored in the Western Australia Antenatal Influenza Vaccination Database. In our cohort, women with a vaccination record in the database with a date of influenza vaccination occurring between the estimated date of conception (based on gestation) and 14 days prior to date of delivery were defined as vaccinated during pregnancy.

Birth Information

The Midwives Notification System is a legally mandated data collection system that requires the healthcare professional attending the birth to provide information at the time of delivery related to the pregnancy for all births in Western Australia ≥20 weeks' gestation [18]. The midwife in attendance usually submits birth information to the system; however, in the absence of a midwife the medical officer is asked to submit the information. If there is no midwife or medical officer in attendance, the first qualified midwife or medical offer to attend would submit the information. In Western Australia, 98% of births occur in hospital (59% of which are public), and 1% occur at a birth center, all of which are staffed by midwives [18]. The remaining 1% of births occur at home, which may or may not be attended by a midwife. The Midwives Notification System is thought to include 99% of births in the state [19]. Midwives Notification System data include the date of birth, birth weight, postcode of residence, status of the baby at birth (alive or dead), Apgar scores at 1 minute and 5 minutes after delivery, medical conditions of the mother, and complications related to the pregnancy and delivery. Gestation provided in Midwives Notification System data is estimated based on a previously validated algorithm drawing from both antenatal indicators (eg, expected due date) and neonatal indicators of gestation (eg, sole creases, scalp hair) [20]. Stillbirth was defined as a birth where the infant was recorded as stillborn by the clinician and had an Apgar score of zero at 1 minute and 5 minutes following birth. This definition is consistent with previously published definitions [21].

Maternal Characteristics

Maternal age, preexisting medical conditions, the occurrence of medical complications during pregnancy (including preeclampsia, gestational diabetes, threatened abortion, threatened preterm labor, and urinary tract infections), and smoking during pregnancy (yes/no) were obtained from the midwives' records. Indigenous status was defined using a previously validated algorithm drawing from multiple government administrative data sets [22]. The statistical local area of the mother at the time of birth was used to calculate a Socio-Economic Indexes for Areas (SEIFA) score. Statistical local areas are Australian Standard Government Classification–defined local areas that cover the whole of Australia. SEIFA is comprised of several indices, the main index being that of the relative disadvantage that is derived from low income, low educational attainment, high unemployment, and jobs in unskilled occupations [23]. SEIFA scores were grouped into quintiles. Statistical local areas were also used to assign individuals into levels of remoteness of their residence based on the Accessibility and Remoteness Index (ARIA) scale, a national index developed by the National Centre for Social Applications of Geographic Information Systems. ARIA scores are based on road distance measurements from the statistical local area of residence to the nearest populated locality >1000 persons; scores range from 1 (highly accessible) to 5 (highly remote) [24].

Statistical Analysis

The odds of vaccination and stillbirth were compared by maternal characteristics using binomial logistic regression models. The odds of stillbirth were also compared by influenza virus circulation at 3 time periods: pre–influenza season, influenza season, and post–influenza season. Pre–influenza season was defined as 1 April–3 June 2012 and 1 January–14 July 2013; influenza season was defined as 4 June–23 September 2012 and 15 July–13 October 2013; and post–influenza season was defined as 24 September–31 December 2012 and 14 October–31 December 2013 (Figure 1). Seasonal cut-points were determined based on statewide notifications for laboratory-confirmed influenza during 2012 and 2013.

Similar to previous investigations [6, 25, 26], we used Cox regression models to compare the risk of stillbirth in vaccinated and unvaccinated women. Days of gestation from 20 weeks was included as the underlying time variable and vaccination status as the time-dependent exposure variable. Because 62% of vaccinated women were immunized after 20 weeks of pregnancy (ie, during the observation period), vaccinated women

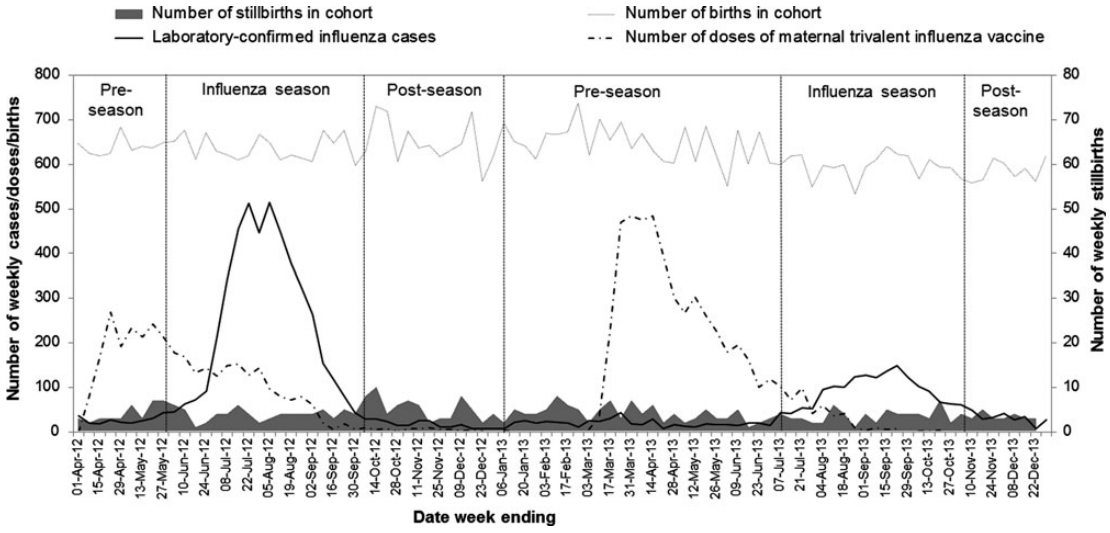

Figure 1. Weekly distribution of live births and stillbirths, doses of seasonal trivalent influenza vaccine, and laboratory-confirmed influenza cases during cohort study period.

contributed unvaccinated person-time until their date of vaccination. Because influenza vaccine uptake was more common in our cohort in women with higher-risk pregnancies [17], models were adjusted by propensity of vaccination to avoid potential confounding by indication. Propensity scores for vaccination were derived from the linear predictor (rather than the predicted probability) of a logistic regression model with maternal age, SEIFA and ARIA scores, primiparity, multiple births, preexisting medical conditions, and complications of pregnancy as independent variables and vaccination status as the dependent variable. Propensity scores ranged from −0.68 to 1.07 (median, 0.23 [interquartile range, 0.05–0.44]). Models were also adjusted for Indigenous status of the mother and self-reported smoking during pregnancy.

To estimate the effect in births following influenza season compared to the effect in births prior to influenza season, we calculated a ratio of hazard ratios (HRs) using the approach outlined by Altman and Bland [27]. Hazards regression models were also created to compare the risk of stillbirth in preterm pregnancies (<37 weeks) and full-term pregnancies (≥37 weeks), and for 5 levels of propensity for vaccination (strata 1, −0.69 to 0.01; strata 2, 0.02–0.15; strata 3, 0.16–0.30; strata 4, 0.31–0.50; strata 5, 0.51–1.07). All covariates were tested to determine whether models met the assumption of proportional hazards ($\alpha = .05$).

RESULTS

A total of 59 333 midwives records were provided for linkage with a date of birth from 1 April 2012 to 31 December 2013. Of these, 1325 were excluded because the mother resided outside Western Australia (n = 71) or had missing covariate information (n = 1254), leaving 58 008 births for analysis. A total of 5541 births were linked to an influenza vaccination record, of which 5076 (92%) had a date of administration ≥14 days prior to the date of delivery. Therefore, the final dataset included 58 008 births, 5076 to vaccinated mothers and 52 932 to unvaccinated mothers (Figure 2), contributing 7 716 084 days of follow-up during pregnancy (462 808 days vaccinated and 7 253 276 days unvaccinated). The majority of births included in the analysis were to mothers who were <35 years of age (80%), non-Indigenous (94%), and in the top 20% socioeconomic (SEIFA) level (65%); 44% resided in a metropolitan area.

Influenza Vaccination

Overall, 8.7% of the cohort received seasonal influenza vaccine during their pregnancy (6.9% in 2012% and 10.2% in 2013). The proportion of births to vaccinated mothers ranged from 0.5% in April 2012 to 15.8% in August 2013, with the number of doses administered to pregnant women peaking in April each year (Figure 1); 18.7% of vaccinated mothers were immunized in the first 13 weeks of pregnancy; 45.7% were immunized in weeks 14–27 of their pregnancy; and 35.6% were immunized in week 28 or later of pregnancy. Vaccination was more common among women >35 years of age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.01–1.15), women residing in highly accessible areas (OR, 2.17; 95% CI, 1.86–2.54), and women in the highest socioeconomic level (OR, 1.25; 95% CI, 1.09–1.45). Women with preexisting medical conditions were more likely to receive an influenza vaccine (OR, 1.46; 95% CI, 1.38–1.54), as were women with preeclampsia (OR, 1.32; 95% CI, 1.11–1.57) or gestational diabetes (OR, 1.34; 95% CI, 1.21–1.48). Primiparous women and women with multiple births were also more likely to be vaccinated compared to multiparous women and women with a singleton pregnancy (OR, 1.14; 95% CI, 1.07–1.21 and OR, 1.35; 95% CI, 1.15–1.58, respectively) (Table 1).

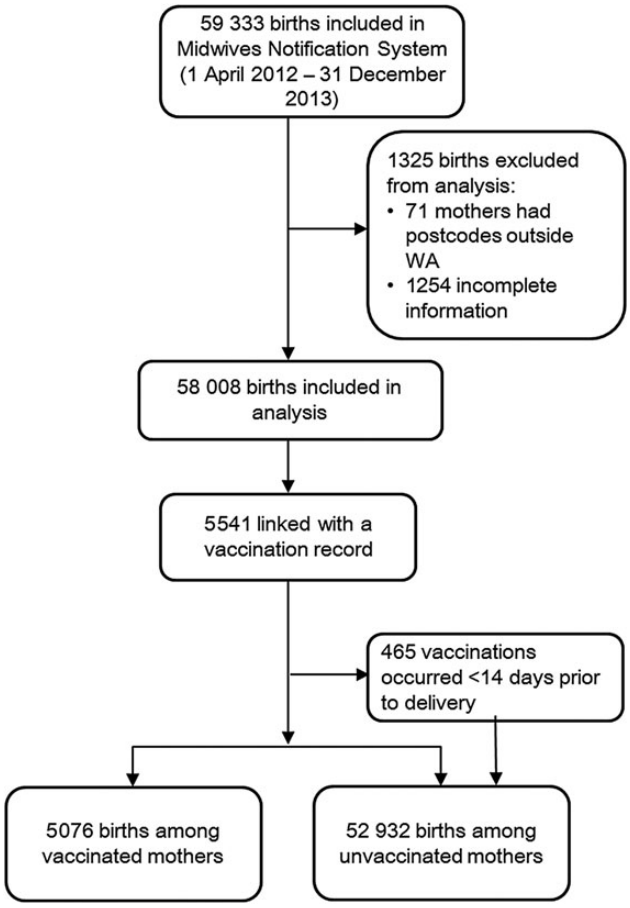

Figure 2. Data linkage of birth cohort, Western Australia (WA), 2012–2013.

Table 1. Antenatal Influenza Vaccination Status of Women Who Delivered in Western Australia Between 1 April 2012 and 31 December 2013, by Demographic Characteristics and Obstetric History[a]

	Percentage Vaccinated		Vaccinated vs Unvaccinated
Characteristic	No.	% (95% CI)	OR (95% CI)[a]
Maternal age			
<35 y	3987	8.6 (8.4–8.9)	Ref
≥35 y	1089	9.2 (8.7–9.8)	1.08 (1.01–1.15)[b]
Indigenous status			
Indigenous	317	9.6 (8.7–10.7)	Ref
Non-Indigenous	4759	8.7 (8.5–8.9)	0.89 (.79–1.01)
Socioeconomic status (SEIFA)			
Quintile 1 (most disadvantaged)	227	7.1 (6.2–8.0)	Ref
Quintile 2	754	8.1 (7.6–8.7)	1.16 (.99–1.35)
Quintile 3	612	7.7 (7.2–8.3)	1.10 (.94–1.29)
Quintile 4	1701	9.9 (9.5–10.3)	1.44 (1.25–1.66)[b]
Quintile 5 (least disadvantaged)	1782	8.7 (8.3–9.1)	1.25 (1.09–1.45)[b]
Remoteness of residence (ARIA)			
Very remote	177	4.9 (4.2–5.7)	Ref
Remote	126	8.0 (6.8–9.5)	1.69 (1.33–2.14)[c]
Moderately accessible	357	7.4 (6.7–8.2)	1.55 (1.29–1.87)[c]
Accessible	1855	8.2 (7.8–8.6)	1.73 (1.48–2.03[c]
Highly accessible	2561	10.1 (9.7–10.5)	2.17 (1.86–2.54)[c]
Preexisting diabetes			
No	5014	8.7 (8.5–8.9)	Ref
Yes	62	14.3 (11.4–18.0)	1.76 (1.34–2.30)[c]
Essential hypertension			
No	5005	8.7 (8.5–8.9)	Ref
Yes	71	11.5 (9.2–14.2)	1.36 (1.06–1.74)[c]
Asthma			
No	4477	8.6 (8.4–8.8)	Ref
Yes	599	10.1 (9.4–10.9)	1.20 (1.10–1.31)[c]
Smoked during pregnancy			
No	4520	8.8 (8.5–9.0)	Ref
Yes	556	8.6 (7.9–9.3)	0.98 (.89–1.07)
Complications during pregnancy[d]			
No	4087	8.4 (8.2–8.7)	Ref
Yes	989	10.5 (9.9–11.2)	1.29 (1.19–1.38)[c]
Type of delivery			
Singleton	4902	8.7 (8.5–8.9)	Ref
Multiple	174	11.3 (9.8–13.0)	1.35 (1.15–1.58)[c]
Parity			
Multiparous	3352	8.4 (8.2–8.7)	Ref
Primiparous	1724	9.5 (9.0–9.9)	1.14 (1.07–1.21)[c]

Abbreviations: ARIA, Accessibility and Remoteness Index of Australia; CI, confidence interval; OR, odds ratio; Ref, reference; SEIFA, Socio-Economic Indexes for Areas.

[a] Shown are the odds of vaccination by select demographic and medical characteristics of mothers as calculated by unconditional logistic regression models.

[b] Significant at $\alpha = .05$.

[c] Significant at $\alpha = .01$.

[d] Complications during pregnancy included preeclampsia, gestational diabetes, threatened preterm abortion, threatened preterm labor, and urinary tract infections.

Stillbirth

During the observation period, 377 stillbirths occurred, equating to 6.5 per 1000 births overall. Stillbirth was more common among women with diabetes (OR, 2.93; 95% CI, 1.44–5.93) or hypertension (OR, 1.92; 95% CI, 1.92–5.88), women who smoked during pregnancy (OR, 1.42; 95% CI, 1.07–1.89), and Indigenous women (OR, 2.04; 95% CI, 1.47–2.83) (Table 2). Stillbirth was less common among women in the highest socioeconomic level (OR, 0.66; 95% CI, .44–.99) and women residing in highly accessible areas (OR, 0.66; 95% CI, .46–.97). Women with a multiple pregnancy had 4 times the odds of stillbirth compared to women with a singleton pregnancy (OR, 4.08; 95% CI, 2.89–5.75). The majority (66.4%) of stillbirths in the cohort occurred between 20 and 27 weeks' gestation. Although not statistically significant, stillbirth was more common during the post–influenza season compared with the pre–influenza season ($P = .07$; Table 2).

The unadjusted incidence of stillbirth in unvaccinated mothers was 5.0 per 100 000 pregnancy-days compared with 3.0 per 100 000 pregnancy-days in vaccinated women (Table 3). The adjusted risk of stillbirth was 51% lower among vaccinated women compared with unvaccinated women (adjusted hazard ratio [aHR], 0.49; 95% CI, .29–.84). Of the 465 women who were vaccinated <14 days before the date of delivery (ie, classified as unvaccinated for this analysis), none had a stillbirth.

Table 2. Stillbirths Recorded in Western Australia Between 1 April 2012 and 31 December 2013, by Maternal Characteristics[a]

Characteristic	Stillbirths per 1000 Pregnancies		Stillbirth vs Live Birth
	No.	No. per 1000 (95% CI)	OR (95% CI)[a]
Maternal age			
<35 y	295	6.4 (5.7–7.2)	Ref
≥35 y	82	6.9 (5.5–8.6)	1.09 (.85–1.39)
Indigenous status			
Indigenous	41	12.5 (9.0–16.9)	Ref
Non-Indigenous	336	6.1 (5.5–6.8)	2.04 (1.47–2.83)[b]
Socioeconomic status (SEIFA)			
Quintile 1 (most disadvantaged)	29	9.1 (6.3–13.0)	Ref
Quintile 2	64	6.9 (5.4–8.8)	0.76 (.49–1.18)
Quintile 3	49	6.2 (4.7–8.2)	0.68 (.43–1.08)
Quintile 4	112	6.5 (5.4–7.8)	0.72 (.48–1.08)
Quintile 5 (least disadvantaged)	123	6.0 (5.0–7.2)	0.66 (.44–.99)[b]
Remoteness of residence (ARIA)			
Very remote	34	9.4 (6.8–13.1)	Ref
Remote	13	8.3 (4.8–14.1)	0.88 (.46–1.67)
Moderately accessible	28	5.8 (4.0–8.4)	0.62 (.37–1.02)
Accessible	142	6.3 (5.3–7.4)	0.66 (.45–.97)[c]
Highly accessible	160	6.3 (5.4–7.4)	0.66 (.46–.97)[c]
Preexisting diabetes			
No	369	6.4 (5.8–7.1)	Ref
Yes	8	18.5 (9.4–36.1)	2.93 (1.44–5.93)[c]
Essential hypertension			
No	364	6.3 (5.7–7.0)	Ref
Yes	13	21.0 (12.3–35.6)	3.36 (1.92–5.88)[c]
Asthma			
No	344	6.6 (5.9–7.3)	Ref
Yes	33	5.6 (4.0–7.8)	0.85 (.59–1.21)
Smoked during pregnancy			
No	320	6.2 (5.6–6.9)	Ref
Yes	57	8.8 (6.8–11.4)	1.42 (1.07–1.89)[c]
Complications during pregnancy[d]			
No	308	6.3 (5.7–7.1)	Ref
Yes	69	7.4 (5.8–9.3)	1.16 (.90–1.51)
Type of delivery			
Singleton	340	6.0 (5.4–6.7)	Ref
Multiple	37	24.1 (17.5–33.1)	4.08 (2.89–5.75)[c]
Parity			
Multiparous	257	6.5 (5.7–7.3)	Ref
Primiparous	120	6.6 (5.5–7.9)	1.02 (.82–1.27)
Influenza season			
Preseason	147	6.2 (5.2–7.2)	Ref
Within season	111	6.1 (5.0–7.3)	0.99 (.77–1.26)
Postseason	119	7.5 (6.3–9.0)	1.22 (.95–1.55)

Abbreviations: ARIA, Accessibility and Remoteness Index of Australia; CI, confidence interval; OR, odds ratio; Ref, reference; SEIFA, Socio-Economic Indexes for Areas.

[a] Shown are the odds of stillbirth by select demographic and medical characteristics of mothers as calculated by unconditional logistic regression models.

[b] Significant at $\alpha = .05$.

[c] Significant at $\alpha = .01$.

[d] Complications during pregnancy included preeclampsia, gestational diabetes, threatened preterm abortion, threatened preterm labor, and urinary tract infections.

When comparing the rate of stillbirth by gestational age, a significant reduction in stillbirths among vaccinated mothers was only observed for stillbirths occurring prior to 37 weeks of gestation (aHR, 0.45; 95% CI, .26–.81). There was a nonsignificant reduction in stillbirth associated with maternal influenza vaccination prior to the start of the influenza season (aHR, 0.60; 95% CI, .22–1.61) and during the influenza season (aHR, 0.57; 95% CI, .25–1.31); however, a greater and significant reduction was observed for births occurring during the post–influenza season period (aHR, 0.33; 95% CI, .12–.88) (Figure 3). The ratio of HRs during the post–influenza season period compared with the pre–influenza season period was 0.55 (95% CI, .13–2.49), suggesting that the effect of vaccination may be greater following influenza season.

DISCUSSION

To our knowledge, this is the first population-based study of seasonal TIV and stillbirth, and the largest cohort study to date evaluating maternal vaccination and stillbirth. We observed a reduced hazard of stillbirth associated with seasonal TIV administered during pregnancy after controlling for risk factors for stillbirth and accounting for factors associated with disproportionate uptake of maternal vaccination. These results are consistent with those of previous large cohort studies investigating the perinatal impact of pandemic and monovalent influenza vaccination in pregnancy [13–16, 26], and support the safety of antenatal administration of seasonal TIV.

Several findings in our study support an association between influenza infection and stillbirth. The observed rate of stillbirth was higher following periods of influenza virus circulation (eg, November–December) compared with periods prior to influenza season (eg, January–May). Although seasonal differences were not statistically significant ($P = .07$), these results suggest a possible temporal association between stillbirth and influenza season. Researchers in Finland observed seasonal patterns in the population incidence of stillbirth, with the highest rates of stillbirth occurring just after influenza season in the northern hemisphere (March) and the lowest rates in summer and autumn [28]. Furthermore, the effect estimate between vaccination and stillbirth was greater during the post–influenza season period compared with the pre–influenza season period. Additional studies should further evaluate the possible temporal association between stillbirth and influenza season.

Our results are consistent with those of previous large cohort studies of maternal influenza vaccination during an influenza pandemic [13–15, 26]. Although observational cohort studies, such as ours, are subject to potential bias, including uncontrolled confounding due to the nature of the study design [13], there are several strengths to this large observational cohort study. First, observational cohort studies are the most efficient method of measuring the impact of maternal influenza vaccination on stillbirth, given the relatively low incidence of stillbirth in developed countries and potentially low uptake of vaccine [13]. With an incidence of 6.4 stillbirths per 1000 births

Table 3. Hazard Ratio of Stillbirth, by Maternal Influenza Vaccination Status[a]

Characteristic	Stillbirths per 100 000 Pregnancy-days		Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[a,b]
	Vaccinated (n = 5076)	Unvaccinated (n = 52 932)		
Total	3.0	5.0	0.52 (.31–.91)[c]	0.49 (.29–.84)[c]
By gestation				
at <37 wk	32.8	67.8	0.43 (.24–.77)[c]	0.45 (.26–.81)[c]
at ≥37 wk	0.5	0.6	1.20 (.29–4.97)	1.13 (.27–4.71)
By propensity for influenza vaccination[d]				
−0.69 to 0.01	1.6	3.4	0.39 (.05–2.79)	0.36 (.05–2.60)
0.02–0.15	3.7	4.6	0.72 (.23–2.29)	0.68 (.21–2.18)
0.16–0.30	3.5	4.1	0.74 (.23–2.38)	0.74 (.23–2.38)
0.31–0.50	2.9	6.3	0.41 (.13–1.30)	0.41 (.13–1.29)
0.51–1.07	3.2	6.7	0.41 (.15–1.13)	0.40 (.15–1.10)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Listed are the incidence and hazard of stillbirth compared by seasonal influenza vaccination status in mothers as calculated based on Cox regression models.

[b] Adjusted analyses controlled for maternal smoking, Indigenous status, and propensity for vaccination.

[c] Significant at $\alpha = .01$.

[d] Propensity scores were calculated based on maternal age, Accessibility and Remoteness Index and Socio-Economic Indexes for Areas scores, primiparity, multiple birth, preexisting medical conditions, and complications of pregnancy as in Table 1.

in Australia [29], other study designs such as randomized controlled trials would be implausible, as well as unethical, given that maternal influenza vaccination is now recommended as standard of care. Second, previous observational cohort studies have taken measures to prevent uncontrolled confounding, including propensity score adjustment [26] and controlling for known maternal risk factors [15], and have observed a significant protective effect of maternal vaccination. Similar to these investigations, we stratified our analyses by the mother's propensity for vaccination and adjusted for known maternal risk factors for stillbirth. Regardless of maternal risk factors and differing predisposition to vaccination, stillbirth was significantly less common in vaccinated mothers compared to unvaccinated.

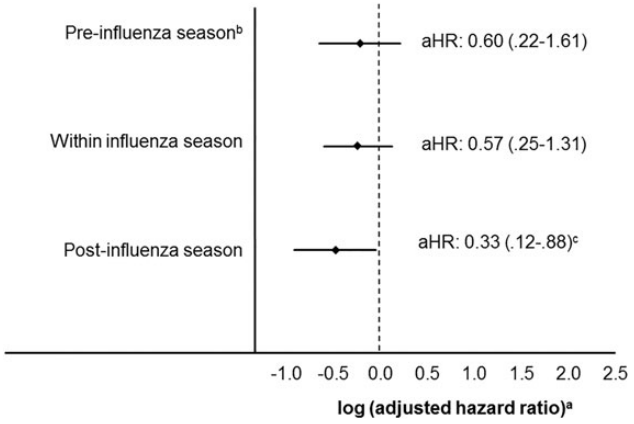

Figure 3. Hazard ratio of stillbirth, by seasonal influenza activity. Depicted are the adjusted hazard ratios (aHRs) and 95% confidence intervals of stillbirth in mothers who had trivalent influenza vaccination compared to unvaccinated mother during pre–influenza season, influenza season, and post–influenza season periods as calculated based on Cox regression models. [a]Hazard ratios were calculated using Cox regression models that adjusted for maternal smoking, Indigenous status, and propensity for vaccination; [b]Influenza season was defined based on statewide laboratory-confirmed influenza notifications. Pre–influenza season included births occurring 1 April–3 June 2012 and 1 January–14 July 2013; influenza season included births occurring 4 June–23 September 2012 and 15 July–13 October 2013; and post–influenza season included births occurring 24 September–31 December 2012 and 14 October–31 December 2013; [c]Significant at $\alpha = .01$.

Despite the strengths of this cohort study, there are several limitations to our cohort which should be considered. Measurement of vaccination status in this cohort is thought to have been incomplete. In the absence of a registry of adult vaccinations in Australia, we relied on provider-reported vaccination events, and there was no legal requirement to report these vaccinations. An evaluation of the completeness of reporting for maternal influenza vaccinations in Western Australia found that approximately half (46%) get reported to the state vaccination database [30]. In addition, a postpartum survey of mothers in Western Australia who delivered in April–October in 2012 and 2013 indicated that 26% and 36% (respectively) had received an influenza vaccination during the study period [17]. In our cohort, 9% and 14% of mothers were reportedly immunized during these respective time periods. However, because false positives (ie, reporting a vaccination when one did not occur) are very unlikely in the vaccination database [30], exposure misclassification in our cohort would likely bias our results toward the null, indicating the protective effect between vaccinations and stillbirths that we observed may be an underestimate of the true effect measure. Second, our cohort was restricted to the Australian setting over 2 influenza seasons; therefore, our results may not be generalizable to developing countries, where stillbirth is more common, or influenza seasons for which the protection afforded by the vaccine might be different. Finally, due to low number of outcomes

in our dataset, we were unable to compare the safety of seasonal influenza vaccine by trimester of administration. Future research should examine whether the lower incidence of stillbirth associated with antenatal influenza vaccinations we observed is applicable to other influenza seasons and settings and across trimesters of vaccine administration.

CONCLUSIONS

Our results support the safety of maternal influenza vaccination, as we found no increase in the risk of stillbirth in vaccinated women. Additional research is needed to confirm the potential reduction in stillbirth observed in this cohort study. There are >3 million stillborn infants each year worldwide, and in developed countries stillbirth accounts for 70% of perinatal deaths [31]; confirmation of these findings would indicate that seasonal influenza vaccination in pregnancy has substantial perinatal health benefits. These results may be useful for communicating the potential benefits of seasonal influenza vaccination to pregnant mothers and their providers. Given the growing body of evidence supporting the health benefits to mother and infant, concerted efforts are needed to improve seasonal influenza vaccine coverage among pregnant women.

Notes

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References

1. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol **2012**; 207:S3–8.
2. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol **2003**; 189:1705–12.
3. Irving WL, James DK, Stephenson T, et al. Influenza virus infection in the second and third trimesters of pregnancy: a clinical and seroepidemiological study. BJOG **2007**; 107:1282–9.
4. Edwards MJ. Review: hyperthermia and fever during pregnancy. Birth Defects Res A Clin Mol Teratol **2006**; 76:507–16.
5. McNeil SA, Dodds LA, Fell DB, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. Am J Obstet Gynecol **2011**; 204:S54–7.
6. Håberg SE, Trogstad L, Gunnes N, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med **2013**; 368:333–40.
7. Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M; UKOSS. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ **2011**; 342: d3214.
8. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med **2008**; 359:1555–64.
9. Thompson MG, Li DK, Shifflett P, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010–2011 and 2011–2012 influenza seasons. Clin Infect Dis **2014**; 58:449–57.
10. Strategic Advisory Group of Experts, World Health Organisation. Background paper on influenza vaccines and immunization. Available at: http://www.who.int/immunization/sage/meetings/2012/april/1_Background_Paper_Mar26_v13_cleaned.pdf. Accessed 30 June 2015.
11. Ding H, Black CL, Ball S, et al. Influenza vaccination coverage among pregnant women – United States, 2013–14 influenza season. MMWR Morb Mortal Wkly Rep **2014**; 63:816–21.
12. Yuen CYS, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women—a systematic review. Vaccine **2014**; 32:4602–13.
13. Fell DB, Platt RW, Lanes A, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. BJOG **2014**; 122:17–26.
14. Fell DB, Sprague AE, Liu N, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health **2012**; 102:33–40.
15. Kallen B, Olausson PO. Vaccination against H1N1 influenza with Pandemrix during pregnancy and delivery outcome: a Swedish register study. BJOG **2012**; 119:1583–90.
16. Bratton KN, Wardle MT, Orenstein WA, Omer SB. Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. Clin Infect Dis **2015**; 60:e11–9.
17. Mak DB, Regan AK, Joyce S, Gibbs R, Effler PV. Antenatal care provider's advice is the key determinant of influenza vaccination uptake in pregnant women. Aust N Z J Obstet Gynaecol **2015**; 55:131–7.
18. Western Australia Department of Health. Western Australia's mothers and babies. Available at: http://www.health.wa.gov.au/publications/documents/perinatal/WA_Mothers_Babies_2011.pdf. Accessed 9 September 2015.
19. Gee V, Dawes V. Validation study of the Western Australian Midwives' Notification System 1992. Western Australia Department of Health; Perth, WA: **1994**. Available at: http://www.health.wa.gov.au/healthdata/docs/Midwives_Validation_Study_1992.pdf. Accessed 9 September 2015.
20. Blair E, Liu Y, Cosgrove P. Choosing the best estimate of gestational age from routinely collected population-based perinatal data. Paediatr Perinat Epidemiol **2004**; 18:270–6.
21. Bukowsi R, Carpenter M, Conway D, et al. Causes of death among stillbirths. JAMA **2011**; 306:2459–68.
22. Christensen D, Davis G, Draper G, et al. Evidence for the use of an algorithm in resolving inconsistent and missing Indigenous status in administrative data collections. Aust J Soc Issues **2014**; 49:423–43.
23. Australian Bureau of Statistics. 2033.0.55.001—Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia 2011. Available at: http://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001. Accessed 1 June 2015.
24. Australian Institute of Health and Welfare. Rural, regional and remote health: a guide to remoteness classifications. Available at: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442459567. Accessed 1 June 2015.
25. Sammon CJ, Snowball J, McGrogan A, de Vries CS. Evaluating the hazard foetal death following H1N1 influenza vaccination; a population-based cohort study in the UK GPRD. PLoS One **2012**; 7:e51734–42.
26. Pasternak B, Svanström H, Mølgaard-Nielsen D, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: a cohort study in Denmark. BMJ **2012**; 344:e2794.
27. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ **2003**; 326:219.
28. Eriksson AW, Fellman J. Seasonal variation of livebirths, stillbirths, extramarital births and twin maternities in Switzerland. Twin Res **2000**; 3:189–201.
29. Australian Institute of Health and Welfare. Australia's mothers and babies 2012. Perinatal statistics series no. 30. Cat. No. PER 69. Available at: http://www.aihw.gov.au/publication-detail/?id=60129550033. Accessed 1 June 2015.
30. Regan AK, Mak DB, Moore HC, et al. Surveillance of antenatal influenza vaccination: validity of current systems and recommendations for improvement. BMC Public Health **2015**; 15:1155.
31. Smith GC, Fretts RC. Stillbirth. Lancet **2007**; 370:1715–25.