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Seasonal trivalent influenza vaccination during pregnancy and the incidence of stillbirth: population-based retrospective cohort study

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Key points:

Concern for the safety to the fetus is a commonly cited reason for vaccine refusal during pregnancy. Results from this investigation support the safety of seasonal influenza vaccination during pregnancy and suggest seasonal influenza vaccination may be protective against stillbirth.

Key words: Stillbirth; seasonal trivalent influenza vaccine; perinatal mortality; maternal immunization

Running title: Stillbirth and maternal influenza vaccination

Abstract

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 below 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 vaccine (TIV).

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 one and five minutes following delivery. Cox regression models adjusted for maternal smoking, Indigenous status and propensity of vaccination were used to calculate adjusted hazard ratios (aHR) in vaccinated and unvaccinated mothers.

Results

A total of 5,076 (8.8%) pregnant women received TIV 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], 0.29 to 0.84). The largest relative reduction in stillbirths was observed for births occurring just after influenza season (aHR, 0.33; 95% CI, 0.12 to 0.88).

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 immunisation during pregnancy and suggest a protective effect.

Background

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] and fetal mortality; this effect has been most pronounced during influenza pandemics.[2,5,6] 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 four-fold increase in stillbirths.[5,7]

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 below 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 to unvaccinated women, supporting the safety of pandemic influenza vaccination during pregnancy;[5,13–16] however, to date, no population-based study has been conducted to evaluate the impact of antenatal administration of seasonal influenza vaccination on stillbirth during non-pandemic 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 approximately 30,000 births each year. For this analysis, multiple state-wide 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 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. Post-partum surveys estimate that 25-36% of women who were pregnant during the study period received seasonal trivalent influenza vaccine.[17] The majority of pregnant women in Australia receive their influenza vaccine from general practitioners; an additional 19% are immunised 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 which 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 centre, 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 one and five 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 (e.g. expected due date) and neonatal indicators of gestation (e.g. 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 one minute and five minutes following birth. This definition is consistent with previously published definitions.[21]

Maternal characteristics

Maternal age, pre-existing medical conditions, the occurrence of medical complications during pregnancy (including pre-eclampsia, gestational diabetes, threatened abortion, threatened preterm labour 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 which cover the whole of Australia. SEIFA is comprised of

several indices, the main index being that of relative disadvantage which 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 greater than 1,000 persons; scores range from one (highly accessible) to five (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 three time periods: pre-influenza season, influenza season, and post-influenza season. Pre-influenza season was defined as 1 Apr - 3 Jun 2012 and 1 Jan - 14 Jul 2013; influenza season was defined as 4 Jun - 23 Sep 2012 and 15 Jul -13 Oct 2013; and post-influenza season was defined as 24 Sep - 31 Dec 2012 and 14 Oct - 31 Dec 2013 (Figure 1). Seasonal cut-points were determined based on state-wide notifications for laboratory-confirmed influenza during 2012 and 2013.

Similar to previous investigations,[5,25–26] 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 immunised after 20 weeks of pregnancy, i.e. during the observation period, vaccinated women 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,[17,21] models were adjusted by propensity of vaccination to avoid potential confounding by indication. Propensity scores for

vaccination were derived from a logistic regression model with maternal age, SEIFA and ARIA scores, primiparity, multiple births, pre-existing 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, IQR: 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 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 five levels of propensity for vaccination (strata 1, -0.69-0.01; 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 (α=.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, 1,325 were excluded because the mother resided outside of Western Australia (n=71) or had missing covariate information (n=1,254), leaving 58,008 births for analysis. A total of 5,541 births were linked to an influenza vaccination record of which 5,076 (92%) had a date of administration 14 days or more prior to the date of delivery. Therefore, the final dataset included 58,008 births, 5,076 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

158 Overall, 8.7% of the cohort received seasonal influenza vaccine during their pregnancy (6.9%
159 in 2012% and 10.2% in 2013). The proportion of births to vaccinated mothers ranged from
160 0.5% in April 2012 to 15.8% in August 2013, with the number of doses administered to
161 pregnant women peaking in April each year (Figure 1); 18.7% of vaccinated mothers were
162 immunised in the first 13 weeks of pregnancy; 45.7% were immunised in weeks 14 to 27 of
163 their pregnancy; and 35.6% were immunised in week 28 or later of pregnancy. Vaccination
164 was more common among women >35 years of age (odds ratio [OR], 1.08; 95% confidence
165 interval [CI], 1.01 to 1.15), women residing in highly accessible areas (OR, 2.17; 95% CI, 1.86
166 to 2.54), and women in the highest socioeconomic level (OR, 1.25; 95% CI, 1.09 to 1.45).
167 Women with pre-existing medical conditions were more likely to receive an influenza vaccine
168 (OR, 1.46; 95% CI, 1.38 to 1.54), as were women with pre-eclampsia (OR, 1.32; 95% CI, 1.11
169 to 1.57) or gestational diabetes (OR, 1.34; 95% CI, 1.21 to 1.48). Primiparous women and
170 women with multiple births were also more likely to be vaccinated compared to multiparous
171 and women with a singleton pregnancy (OR, 1.14; 95% CI, 1.07 to 1.21 and OR, 1.35; 95%
172 CI, 1.15 to 1.58, respectively) (Table 1).

173 **Stillbirth**

174 During the observation period, 377 stillbirths occurred, equating to 6.5 per 1,000 births overall.
175 Stillbirth was more common among women with diabetes (OR, 2.93; 95% CI, 1.44 to 5.93) or
176 hypertension (OR, 1.92; 95% CI, 1.92 to 5.88), women who smoked during pregnancy (OR,
177 1.42; 95% CI, 1.07 to 1.89), and Indigenous women (OR, 2.04; 95% CI, 1.47 to 2.83) (Table
178 2). Stillbirth was less common among women in the highest socioeconomic level (OR, 0.66;
179 95% CI, 0.44 to 0.99) and women residing in highly accessible areas (OR, 0.66; 95% CI, 0.46
180 to 0.97). Women with a multiple pregnancy had four times the odds of stillbirth compared to
181 women with a singleton pregnancy (OR, 4.08; 95% CI, 2.89 to 5.75). The majority (66.4%) of
182 stillbirths in the cohort occurred between 20 and 27 weeks gestation. Although not statistically
183 significant, stillbirth was more common during post-influenza season compared with pre-
184 influenza season (p=0.07) (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 to unvaccinated women (adjusted hazard ratio (aHR), 0.49; 95% CI, 0.29 to 0.84). Of the 465 women who were vaccinated <14 days before the date of delivery, i.e. classified as unvaccinated for this analysis, none had a stillbirth. 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, 0.26 to 0.81). There was a non-significant reduction in stillbirth associated with maternal influenza vaccination prior to the start of the influenza season (aHR, 0.60; 95% CI, 0.22 to 1.61) and during the influenza season (aHR, 0.57; 95% CI, 0.25 to 1.31); however, a greater and significant reduction was observed for births occurring during the post-influenza season period (aHR, 0.33; 95% CI, 0.12 to 0.88) (Figure 3). The ratio of hazards ratios during the post-influenza season period compared to the pre-influenza season period was 0.55 (95% CI, 0.13 to 2.49), suggesting the effect of vaccination may be greater following influenza season.

Discussion

To our knowledge, this is the first population-based study of seasonal trivalent influenza vaccine and stillbirth, and the largest cohort study to date evaluating maternal vaccination and stillbirth. We observed a reduced hazard of stillbirth associated with seasonal trivalent influenza vaccine 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 trivalent influenza vaccine.

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 (e.g. November through December) compared to periods prior to influenza season (e.g. January through May). Although seasonal differences were not statistically significant (p=0.07), 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 to 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 1,000 births in Australia,[29] other study designs such as randomised 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.

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 post-partum survey of mothers in Western Australia who delivered in April through 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 immunised during these respective time periods. However, because false positives (i.e. 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 two 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 over three million stillborn infants

each year worldwide, and in developed countries stillbirth accounts for 70% of perinatal deaths;[31] confirmation of these findings would indicate 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.

Author Contributions

AR performed all data management and analysis and led the writing of the manuscript; NK, HM, SO, and PE each contributed to the study design, interpretation of data, and writing of the manuscript. GS and DM contributed to the study design and writing of the manuscript.

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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.*

Characteristic	Percent vaccinated		Vaccinated versus Unvaccinated
Maternal age	n	% (95% CI)	OR (95% CI)*
<35 years	3,987	8.6 (8.4-8.9)	Ref
≥35 years	1,089	9.2 (8.7-9.8)	1.08 (1.01-1.15) †
Indigenous status			
Indigenous	317	9.6 (8.7-10.7)	Ref
Non-Indigenous	4,759	8.7 (8.5-8.9)	0.89 (0.79-1.01)
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 (0.99-1.35)
Quintile 3	612	7.7 (7.2-8.3)	1.10 (0.94-1.29)
Quintile 4	1,701	9.9 (9.5-10.3)	1.44 (1.25-1.66) †
Quintile 5 (least disadvantaged)	1,782	8.7 (8.3-9.1)	1.25 (1.09-1.45) †
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)‡
Moderately accessible	357	7.4 (6.7-8.2)	1.55 (1.29-1.87) ‡
Accessible	1,855	8.2 (7.8-8.6)	1.73 (1.48-2.03 ‡
Highly accessible	2,561	10.1 (9.7-10.5)	2.17 (1.86-2.54)‡
Pre-existing diabetes			
No	5,014	8.7 (8.5-8.9)	Ref
Yes	62	14.3 (11.4-18.0)	1.76 (1.34-2.30)‡
Essential hypertension			

No	5,005	8.7 (8.5-8.9)	Ref
Yes	71	11.5 (9.2-14.2)	1.36 (1.06-1.74)‡
Asthma			
No	4,477	8.6 (8.4-8.8)	Ref
Yes	599	10.1 (9.4-10.9)	1.20 (1.10-1.31)‡
Smoked during pregnancy			
No	4,520	8.8 (8.5-9.0)	Ref
Yes	556	8.6 (7.9-9.3)	0.98 (0.89-1.07)
Complications during pregnancy§			
No	4,087	8.4 (8.2-8.7)	Ref
Yes	989	10.5 (9.9-11.2)	1.29 (1.19-1.38)‡
Type of delivery			
Singleton	4,902	8.7 (8.5-8.9)	Ref
Multiple	174	11.3 (9.8-13.0)	1.35 (1.15-1.58) ‡
Parity			
Multiparous	3,352	8.4 (8.2-8.7)	Ref
Primiparous	1,724	9.5 (9.0-9.9)	1.14 (1.07-1.21) ‡

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

†Significant at α=.05

‡Significant at α=.01

§ Complications during pregnancy included pre-eclampsia, gestational diabetes, threatened preterm abortion, threatened preterm labour, and urinary tract infections.

Table 2. Stillbirths recorded in Western Australia between 1 April 2012 and 31 December 2013, by maternal characteristics.*

Characteristic	Stillbirths per 1,000 pregnancies		Stillbirth vs live birth
Maternal age	n	No. per 1,000 (95% CI)	OR (95% CI)*
<35 years	295	6.4 (5.7-7.2)	Ref
≥35 years	82	6.9 (5.5-8.6)	1.09 (0.85-1.39)
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)†
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 (0.49-1.18)
Quintile 3	49	6.2 (4.7-8.2)	0.68 (0.43-1.08)
Quintile 4	112	6.5 (5.4-7.8)	0.72 (0.48-1.08)
Quintile 5 (least disadvantaged)	123	6.0 (5.0-7.2)	0.66 (0.44-0.99) †
Remoteness of residence (ARIA)			
Very remote	34	9.4 (6.8-13.1)	Ref
Remote	13	8.3 (4.8-14.1)	0.88 (0.46-1.67)
Moderately accessible	28	5.8 (4.0-8.4)	0.62 (0.37-1.02)
Accessible	142	6.3 (5.3-7.4)	0.66 (0.45-0.97)‡
Highly accessible	160	6.3 (5.4-7.4)	0.66 (0.46-0.97)‡
Pre-existing diabetes			
No	369	6.4 (5.8-7.1)	Ref
Yes	8	18.5 (9.4-36.1)	2.93 (1.44-5.93) ‡
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) ‡
Asthma			
No	344	6.6 (5.9-7.3)	Ref
Yes	33	5.6 (4.0-7.8)	0.85 (0.59-1.21)
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) ‡
Complications during pregnancy			
No	308	6.3 (5.7-7.1)	Ref
Yes	69	7.4 (5.8-9.3)	1.16 (0.90-1.51)
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)‡
Parity			
Multiparous	257	6.5 (5.7-7.3)	Ref
Primiparous	120	6.6 (5.5-7.9)	1.02 (0.82-1.27)
Influenza season			
Pre-season	147	6.2 (5.2-7.2)	Ref
Within season	111	6.1 (5.0-7.3)	0.99 (0.77-1.26)
Post-season	119	7.5 (6.3-9.0)	1.22 (0.95-1.55)

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

†Significant at α=.05

‡Significant at α=.01

§ Complications during pregnancy included pre-eclampsia, gestational diabetes, threatened preterm abortion, threatened preterm labour, and urinary tract infections.

Table 3. Hazard ratio of stillbirth, by maternal influenza vaccination status*

	Vaccinated (n=5,076)	Unvaccinated (n=52,932)	Hazard Ratio (95% CI)*	
	Stillbirths per 100,000 pregnancy days	Stillbirths per 100,000 pregnancy days	Unadjusted	Adjusted†
TOTAL	3.0	5.0	0.52 (0.31-0.91)§	0.49 (0.29-0.84)§
By gestation				
at <37 weeks	32.8	67.8	0.43 (0.24-0.77)§	0.45 (0.26-0.81)§
at ≥37 weeks	0.5	0.6	1.20 (0.29-4.97)	1.13 (0.27-4.71)
By propensity for influenza vaccination§§				
-0.69-0.01	1.6	3.4	0.39 (0.05-2.79)	0.36 (0.05-2.60)
0.02-0.15	3.7	4.6	0.72 (0.23-2.29)	0.68 (0.21-2.18)
0.16-0.30	3.5	4.1	0.74 (0.23-2.38)	0.74 (0.23-2.38)
0.31-0.50	2.9	6.3	0.41 (0.13-1.30)	0.41 (0.13-1.29)
0.51-1.07	3.2	6.7	0.41 (0.15-1.13)	0.40 (0.15-1.10)

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

† Adjusted analyses controlled for maternal smoking, Indigenous status, and propensity for vaccination.

§Significant at α=.01

¶Significant at α=.05

§§ Propensity scores were calculated based on maternal age, SEIFA and ARIA score, primiparity, multiple birth, pre-existing medical conditions, and complications of pregnancy as in Table 1.

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

Figure 2. Data linkage of birth cohort – Western Australia, Australia, 2012-13.

Figure 3. Hazard ratio of stillbirth, by seasonal influenza activity*

Figure 3 footnotes:

*Depicted are the hazard ratios of stillbirth in mothers who had trivalent influenza vaccination compare to unvaccinated mother during pre-influenza, influenza, and post-influenza periods as calculated based on Cox regression models.

†Hazard ratios were calculated using Cox regression models which adjusted for maternal smoking, Indigenous status, and propensity for vaccination.

§ Influenza season was defined based on state-wide laboratory-confirmed influenza notifications. Pre-influenza season included births occurring between 01Apr2012-03Jun2012 and 01Jan2013-14Jul2013, influenza season included births occurring between 04Jun2012-23Sep2012 and 15Jul2013-13Oct2013, and post-influenza season included births occurring between 24Sep2012-31Dec2012 and 14Oct2013-31Dec2013.

¶ Significant at α=.01.

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