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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

1 **Abstract**

2 **Background**

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

9 **Methods**

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

16 **Results**

17 A total of 5,076 (8.8%) pregnant women received TIV and 377 stillbirths occurred. There were
18 5.0 and 3.0 stillbirths per 100,000 pregnancy days among unvaccinated and vaccinated
19 women, respectively. After adjustment, stillbirth was 51% less likely among vaccinated vs
20 unvaccinated mothers (aHR, 0.49; 95% confidence interval [CI], 0.29 to 0.84). The largest
21 relative reduction in stillbirths was observed for births occurring just after influenza season
22 (aHR, 0.33; 95% CI, 0.12 to 0.88).

23 **Conclusions**

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

27 **Background**

28 Pregnant women are at increased risk of serious complications following influenza infection,
29 including pneumonia and acute respiratory distress syndrome.¹⁻³ This increased risk is
30 thought to be the result of depressed cell-mediated immunity and physiological changes to the
31 cardiopulmonary system associated with pregnancy.^{1,3} Influenza infection during pregnancy
32 has also been linked to adverse fetal and neonatal outcomes, including increased risk of
33 preterm birth^{1,4} and fetal mortality; this effect has been most pronounced during influenza
34 pandemics.^{2,5,6} During the recent 2009 influenza A/H1N1 pandemic, a significant increase in
35 perinatal mortality was observed following maternal infection, most of this attributable to a
36 four-fold increase in stillbirths.^{5,7}

37
38 Seasonal influenza vaccination has been shown to prevent infection in mothers and their
39 newborn infants,^{8,9} and the World Health Organization has indicated that pregnant women
40 should receive the highest priority for seasonal influenza vaccination.¹⁰ Reported vaccine
41 uptake remains below 50% in pregnant women, and concern regarding the safety of the
42 vaccine for the fetus is a commonly cited reason why women refuse vaccination.¹¹⁻¹²
43 Enhanced data collection and surveillance during the 2009 H1N1 pandemic offered the unique
44 opportunity to monitor the safety of pandemic influenza vaccination in large, observational
45 studies.¹³ These studies suggested stillbirth was less common in women who received
46 pandemic vaccine compared to unvaccinated women, supporting the safety of pandemic
47 influenza vaccination during pregnancy,^{5,13-16} however, to date, no population-based study
48 has been conducted to evaluate the impact of antenatal administration of seasonal influenza
49 vaccination on stillbirth during non-pandemic influenza seasons.^{13,16} The aim of this study was
50 to assess the relative risk of stillbirth among vaccinated and unvaccinated pregnant women
51 during the 2012 and 2013 seasonal influenza epidemics in the winter months of the southern
52 hemisphere.

53 **Methods**

54 Western Australia has a population of 2.4 million people, with 71% residing in the Perth
55 metropolitan area. There are approximately 30,000 births each year. For this analysis, multiple
56 state-wide data sources were linked by the Western Australian Data Linkage Branch of the
57 Western Australia Department of Health, using probabilistic matching of the full name and date
58 of birth of mothers who delivered in Western Australia between 1 April 2012 and 31 December
59 2013. The project was approved by the Western Australia Department of Health Human
60 Research Ethics Committee.

61 **Data sources**

62 **Vaccination status**

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

76

77

78 **Birth information**

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

97 **Maternal characteristics**

98 Maternal age, pre-existing medical conditions, the occurrence of medical complications during
99 pregnancy (including pre-eclampsia, gestational diabetes, threatened abortion, threatened
100 preterm labour and urinary tract infections), and smoking during pregnancy (yes/no) were
101 obtained from the midwives' records. Indigenous status was defined using a previously
102 validated algorithm drawing from multiple government administrative data sets.²² The
103 statistical local area of the mother at the time of birth was used to calculate a Socio-Economic
104 Indexes for Areas (SEIFA) score. Statistical local areas are Australian Standard Government
105 Classification defined local areas which cover the whole of Australia. SEIFA is comprised of

106 several indices, the main index being that of relative disadvantage which is derived from low
107 income, low educational attainment, high unemployment and jobs in unskilled
108 occupations.²³ SEIFA scores were grouped into quintiles. Statistical local areas were also used
109 to assign individuals into levels of remoteness of their residence based on the Accessibility
110 and Remoteness Index (ARIA) scale, a national index developed by the National Centre for
111 Social Applications of Geographic Information Systems. ARIA scores are based on road
112 distance measurements from the statistical local area of residence to the nearest populated
113 locality greater than 1,000 persons; scores range from one (highly accessible) to five (highly
114 remote).²⁴

115 **Statistical analysis**

116 The odds of vaccination and stillbirth were compared by maternal characteristics using
117 binomial logistic regression models. The odds of stillbirth were also compared by influenza
118 virus circulation at three time periods: pre-influenza season, influenza season, and post-
119 influenza season. Pre-influenza season was defined as 1 Apr - 3 Jun 2012 and 1 Jan - 14 Jul
120 2013; influenza season was defined as 4 Jun - 23 Sep 2012 and 15 Jul -13 Oct 2013; and
121 post-influenza season was defined as 24 Sep - 31 Dec 2012 and 14 Oct - 31 Dec 2013 (Figure
122 1). Seasonal cut-points were determined based on state-wide notifications for laboratory-
123 confirmed influenza during 2012 and 2013.

124

125 Similar to previous investigations,^{5,25-26} we used Cox regression models to compare the risk
126 of stillbirth in vaccinated and unvaccinated women. Days of gestation from 20 weeks was
127 included as the underlying time variable and vaccination status as the time-dependent
128 exposure variable. Because 62% of vaccinated women were immunised after 20 weeks of
129 pregnancy, i.e. during the observation period, vaccinated women contributed unvaccinated
130 person-time until their date of vaccination. Because influenza vaccine uptake was more
131 common in our cohort in women with higher risk pregnancies,^{17,21} models were adjusted by
132 propensity of vaccination to avoid potential confounding by indication. Propensity scores for

133 vaccination were derived from a logistic regression model with maternal age, SEIFA and ARIA
134 scores, primiparity, multiple births, pre-existing medical conditions, and complications of
135 pregnancy as independent variables and vaccination status as the dependent variable.
136 Propensity scores ranged from -0.68 to 1.07 (median: 0.23, IQR: 0.05, 0.44). Models were
137 also adjusted for Indigenous status of the mother and self-reported smoking during pregnancy.

138

139 To estimate the effect in births following influenza season compared to the effect in births prior
140 to influenza season, we calculated a ratio of hazard ratios using the approach outlined by
141 Altman and Bland.²⁷ Hazards regression models were also created to compare the risk of
142 stillbirth in preterm pregnancies (<37 weeks) and full-term pregnancies (≥37 weeks), and for
143 five levels of propensity for vaccination (strata 1, -0.69-0.01; strata 2, 0.02-0.15; strata 3, 0.16-
144 0.30; strata 4, 0.31-0.50; strata 5, 0.51-1.07). All covariates were tested to determine whether
145 models met the assumption of proportional hazards ($\alpha=0.05$).

146 **Results**

147 A total of 59,333 midwives records were provided for linkage with a date of birth from 1 April
148 2012 to 31 December 2013. Of these, 1,325 were excluded because the mother resided
149 outside of Western Australia (n=71) or had missing covariate information (n=1,254), leaving
150 58,008 births for analysis. A total of 5,541 births were linked to an influenza vaccination record
151 of which 5,076 (92%) had a date of administration 14 days or more prior to the date of delivery.
152 Therefore, the final dataset included 58,008 births, 5,076 to vaccinated mothers and 52,932
153 to unvaccinated mothers (Figure 2), contributing 7,716,084 days of follow-up during pregnancy
154 (462,808 days vaccinated and 7,253,276 days unvaccinated). The majority of births included
155 in the analysis were to mothers who were <35 years of age (80%), non-Indigenous (94%), and
156 in the top 20% socioeconomic (SEIFA) level (65%); 44% resided in a metropolitan area.

157 **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).

185

186 The unadjusted incidence of stillbirth in unvaccinated mothers was 5.0 per 100,000 pregnancy
187 days compared with 3.0 per 100,000 pregnancy days in vaccinated women (Table 3). The
188 adjusted risk of stillbirth was 51% lower among vaccinated women compared to unvaccinated
189 women (adjusted hazard ratio (aHR), 0.49; 95% CI, 0.29 to 0.84). Of the 465 women who
190 were vaccinated <14 days before the date of delivery, i.e. classified as unvaccinated for this
191 analysis, none had a stillbirth. When comparing the rate of stillbirth by gestational age, a
192 significant reduction in stillbirths among vaccinated mothers was only observed for stillbirths
193 occurring prior to 37 weeks of gestation (aHR, 0.45; 95% CI, 0.26 to 0.81). There was a non-
194 significant reduction in stillbirth associated with maternal influenza vaccination prior to the start
195 of the influenza season (aHR, 0.60; 95% CI, 0.22 to 1.61) and during the influenza season
196 (aHR, 0.57; 95% CI, 0.25 to 1.31); however, a greater and significant reduction was observed
197 for births occurring during the post-influenza season period (aHR, 0.33; 95% CI, 0.12 to 0.88)
198 (Figure 3). The ratio of hazards ratios during the post-influenza season period compared to
199 the pre-influenza season period was 0.55 (95% CI, 0.13 to 2.49), suggesting the effect of
200 vaccination may be greater following influenza season.

201 **Discussion**

202 To our knowledge, this is the first population-based study of seasonal trivalent influenza
203 vaccine and stillbirth, and the largest cohort study to date evaluating maternal vaccination and
204 stillbirth. We observed a reduced hazard of stillbirth associated with seasonal trivalent
205 influenza vaccine administered during pregnancy after controlling for risk factors for stillbirth
206 and accounting for factors associated with disproportionate uptake of maternal vaccination.
207 These results are consistent with those of previous large cohort studies investigating the
208 perinatal impact of pandemic and monovalent influenza vaccination in pregnancy^{13-16,26} and
209 support the safety of antenatal administration of seasonal trivalent influenza vaccine.

210

211 Several findings in our study support an association between influenza infection and stillbirth.
212 The observed rate of stillbirth was higher following periods of influenza virus circulation (e.g.
213 November through December) compared to periods prior to influenza season (e.g. January
214 through May). Although seasonal differences were not statistically significant ($p=0.07$), these
215 results suggest a possible temporal association between stillbirth and influenza season.
216 Researchers in Finland observed seasonal patterns in the population incidence of stillbirth,
217 with the highest rates of stillbirth occurring just after influenza season in the northern
218 hemisphere (March) and the lowest rates in summer and autumn.²⁸ Furthermore, the effect
219 estimate between vaccination and stillbirth was greater during the post-influenza season
220 period compared to the pre-influenza season period. Additional studies should further evaluate
221 the possible temporal association between stillbirth and influenza season.

222

223 Our results are consistent with those of previous large cohort studies of maternal influenza
224 vaccination during an influenza pandemic.^{13–15,26} Although observational cohort studies, such
225 as ours, are subject to potential bias, including uncontrolled confounding due to the nature of
226 the study design,¹³ there are several strengths to this large observational cohort study. First,
227 observational cohort studies are the most efficient method of measuring the impact of maternal
228 influenza vaccination on stillbirth, given the relatively low incidence of stillbirth in developed
229 countries and potentially low uptake of vaccine.¹³ With an incidence of 6.4 stillbirths per 1,000
230 births in Australia,²⁹ other study designs such as randomised controlled trials would be
231 implausible, as well as unethical, given that maternal influenza vaccination is now
232 recommended as standard of care. Second, previous observational, cohort studies have taken
233 measures to prevent uncontrolled confounding, including propensity score adjustment²⁶ and
234 controlling for known maternal risk factors,¹⁵ and have observed a significant protective effect
235 of maternal vaccination. Similar to these investigations, we stratified our analyses by the
236 mother's propensity for vaccination and adjusted for known maternal risk factors for stillbirth.
237 Regardless of maternal risk factors and differing predisposition to vaccination, stillbirth was
238 significantly less common in vaccinated mothers compared to unvaccinated.

239

240 Despite the strengths of this cohort study, there are several limitations to our cohort which
241 should be considered. Measurement of vaccination status in this cohort is thought to have
242 been incomplete. In the absence of a registry of adult vaccinations in Australia, we relied on
243 provider-reported vaccination events and there was no legal requirement to report these
244 vaccinations. An evaluation of the completeness of reporting for maternal influenza
245 vaccinations in Western Australia found that approximately half (46%) get reported to the state
246 vaccination database.³⁰ In addition, a post-partum survey of mothers in Western Australia who
247 delivered in April through October in 2012 and 2013 indicated that 26% and 36% (respectively)
248 had received an influenza vaccination during the study period.¹⁷ In our cohort, 9% and 14% of
249 mothers were reportedly immunised during these respective time periods. However, because
250 false positives (i.e. reporting a vaccination when one did not occur) are very unlikely in the
251 vaccination database,³⁰ exposure misclassification in our cohort would likely bias our results
252 toward the null, indicating the protective effect between vaccinations and stillbirths that we
253 observed may be an underestimate of the true effect measure. Second, our cohort was
254 restricted to the Australian setting over two influenza seasons; therefore our results may not
255 be generalizable to developing countries, where stillbirth is more common, or influenza
256 seasons for which the protection afforded by the vaccine might be different. Finally, due to low
257 number of outcomes in our dataset, we were unable to compare the safety of seasonal
258 influenza vaccine by trimester of administration. Future research should examine whether the
259 lower incidence of stillbirth associated with antenatal influenza vaccinations we observed is
260 applicable to other influenza seasons and settings and across trimesters of vaccine
261 administration.

262 **Conclusions**

263 Our results support the safety of maternal influenza vaccination, as we found no increase in
264 the risk of stillbirth in vaccinated women. Additional research is needed to confirm the potential
265 reduction in stillbirth observed in this cohort study. There are over three million stillborn infants

266 each year worldwide, and in developed countries stillbirth accounts for 70% of perinatal
267 deaths;³¹ confirmation of these findings would indicate seasonal influenza vaccination in
268 pregnancy has substantial perinatal health benefits. These results may be useful for
269 communicating the potential benefits of seasonal influenza vaccination to pregnant mothers
270 and their providers. Given the growing body of evidence supporting the health benefits to
271 mother and infant, concerted efforts are needed to improve seasonal influenza vaccine
272 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
	n	% (95% CI)	OR (95% CI)*
Maternal age			
<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 $\alpha=.05$

[‡]Significant at $\alpha=.01$

[§] 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
	n	No. per 1,000 (95% CI)	OR (95% CI)*
Maternal age			
<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 $\alpha=.05$

[‡]Significant at $\alpha=.01$

[§]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)*	
			Unadjusted	Adjusted [†]
	Stillbirths per 100,000 pregnancy days	Stillbirths per 100,000 pregnancy days		
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 $\alpha=.01$

[†]Significant at $\alpha=.05$

^{§§} 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 $\alpha=.01$.

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. 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.
6. 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.
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 June 30, 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 September 9, 2015.
19. Gee V, Dawes V. Validation study of the Western Australian Midwives' Notification System 1992. Western Australia Department of Health; Perth WA: July 1994. Available at: http://www.health.wa.gov.au/healthdata/docs/Midwives_Validation_Study_1992.pdf
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. Bukowski 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>, 2013. Accessed June 1, 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 June 1, 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 June 1, 2015.
30. Regan AK, Mak DB, Moore HC, Tracey L, Saker R, Jones C, Effler PV. 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.