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Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood

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ABSTRACT

Background: Influenza vaccination is recommended to protect mothers and their infants from influenza infection. Few studies have evaluated the health impacts of *in utero* exposure to influenza vaccine among children more than six months of age.
Methods: We used probabilistically linked administrative health records to establish a mother–child cohort to evaluate the risk of influenza and acute respiratory infections associated with maternal influenza vaccination. Outcomes were laboratory-confirmed influenza (LCI) and hospitalization for influenza or acute respiratory infection (ARI). Adjusted hazard ratios (aHRs) accounted for child's Aboriginal status and were weighted by the inverse-probability of treatment.
Results: 14,396 (11.5%) children were born to vaccinated mothers. Maternally vaccinated infants aged < 6 months had lower risk of LCI (aHR: 0.33; 95% CI: 0.13, 0.85), influenza-associated hospitalization (aHR: 0.39; 95% CI: 0.16, 0.94) and ARI-associated hospitalization (aHR: 0.85; 95% CI: 0.77, 0.94) compared to maternally unvaccinated infants. With the exception of an increased risk of LCI among children aged 6 months to < 2 years old following first trimester vaccination (aHR: 2.28; 95% CI: 1.41, 3.69), there were no other differences in the risk of LCI, influenza-associated hospitalization or ARI-associated hospitalization among children aged > 6 months.
Conclusion: Study results show that maternal influenza vaccination is effective in preventing influenza in the first six months and had no impact on respiratory infections after two years of age.

1. Introduction

Influenza causes serious morbidity and mortality through seasonal epidemics each year, particularly in children under the age of five years [1,2]. Although the best preventative tool for influenza is seasonal influenza vaccination [3], there are currently no influenza vaccines licensed for use for infants aged < 6 months [2]. Since maternal antibodies cross the placenta during pregnancy [4], prenatal administration of seasonal inactivated influenza vaccine (IIV) is recommended for pregnant women in many countries, including Australia, at any stage of pregnancy to protect both mothers and their newborns from influenza illness during their first few months of life [2,5].

Several studies have found that maternal influenza vaccination is effective in reducing the risk of laboratory-confirmed influenza (LCI) illness and acute respiratory infections (ARIs) in young infants [6,7]. A systematic review and meta-analysis of four randomized controlled trials and five observational studies reported a lower risk of LCI infection by 48% and lower risk of LCI-associated hospitalizations by 72% among children aged less than six months following maternal influenza vaccination [6]. However, few studies have evaluated the risk of LCI infection beyond six months of age among maternally vaccinated offspring [8]. Maternally-acquired antibodies have been known to "blunt" or dampen primary immune responses to infection or vaccination [9,10]. Although seven studies identified no difference in the risk of acute respiratory infections through five years of age [8], no study has evaluated the risk of LCI after 12 months of age [8].

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The aim of the present study was to measure the association between *in utero* exposure to seasonal IIV and the occurrence of ARIs, including LCI, from birth to five years of age.

2. Methods

2.1. Study setting

Western Australia (WA) has a resident population of approximately 2.6 million people [11], with approximately 33,000 births in WA each year [12]. In Australia, seasonal IIV during pregnancy has been recommended by the Australian Technical Advisory Group on Immunisation since March 2000 and funded under the National Immunisation Program since January 2010 [5,13]. Influenza virus circulation tends to peak during the winter months (June-August), with less distinct seasonality in the northern areas of the state; seasonal influenza vaccines are typically available in April of each year [14].

2.2. Study design, population, and data sources

We conducted a retrospective, population-based cohort study. The cohort included all singleton, live-born children identified from birth registrations between 1 April 2012 and 1 July 2016 and their mothers (Fig. 1). These mother-infant pairs were probabilistically linked with other population-based administrative health datasets using best practice protocols through the WA Data Linkage Branch [15], including the Midwives Notification System (MNS) [16], WA Antenatal Vaccination Database (WAAVD) [17], WA Notifiable Infectious Diseases Database (WANIDD) [18], Hospital Morbidity Data Collection (HMDC) [19], and death registrations. This study and a waiver of consent was approved by the WA Department of Health (RA#2016.56) and the Curtin University Human Research Ethics Committee (RA#20217–0808).

The MNS is a legally-mandated perinatal data collection of all births $\geq$ 20 weeks gestation or birthweight of $\geq$ 400 g (where gestational age is unknown). The MNS includes maternal demographics and health information, obstetric history, date of delivery, gestational age, and birthweight. The WAAVD is a state-wide database, managed by the WA Department of Health, and includes the date of vaccination, vaccine brand and batch number, and the estimated gestation at which vaccinations were administered as reported by their healthcare provider.

WANIDD is a legally-mandated database of notifiable infectious diseases reported to the WA Department of Health. In Australia, LCI is a notifiable disease and WANIDD includes information on the date of specimen collection, laboratory method of confirmation, and virus type/subtype. The HMDC summarizes all episodes of care provided in the state's public and private hospitals. Information details the date of admission and separation, up to 21 diagnosis codes (classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] codes) [19]. Death registrations include the date and cause of all registered deaths in the state.

2.3. Exposure measurement

Children whose mothers had a record of receipt of prenatal seasonal IIV were considered 'maternally vaccinated'. We estimated the gestational age at vaccination as the number of completed weeks from estimated date of conception to date of vaccination. Trimesters were categorized as: first trimester (0 to $\leq$ 13 weeks gestation), second trimester (14 to $\leq$ 27 weeks gestation), and third trimester ($\geq$ 28 weeks gestation). Children of mothers with no vaccination record were considered 'maternally unvaccinated'. Children whose mothers received an influenza vaccine < 2 weeks prior to birth were considered to have 'indeterminate' vaccination status and were excluded from analysis.

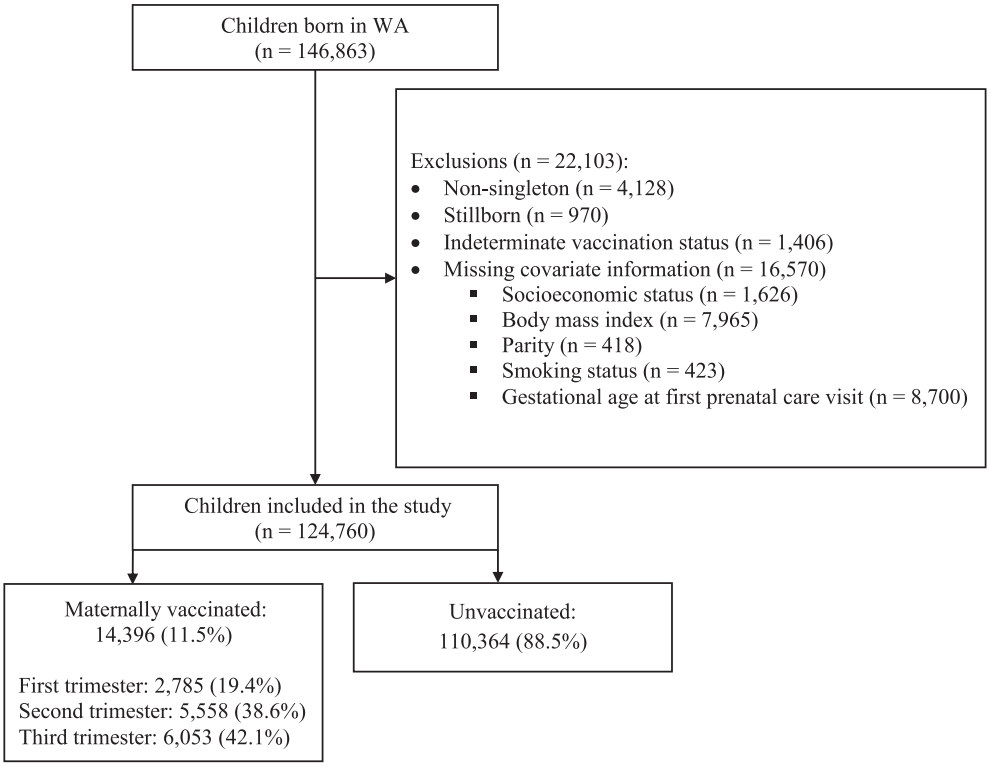

Fig. 1. Flow diagram of study participants included in the cohort.

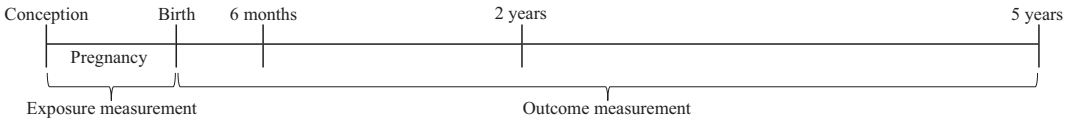

Fig. 2. Timing of exposure measurement and outcome measurement. Exposure: maternal influenza vaccination; outcome: laboratory-confirmed influenza, influenza-associated hospitalization, acute respiratory infection-associated hospitalization, all-cause injury-associated hospitalization, or skin infection-associated hospitalization.

2.4. Outcome measurement

We assessed three primary outcomes: 1) LCI, as reported to WANIDD, 2) influenza-associated hospitalizations, and 3) ARI-associated hospitalizations. We defined influenza-associated hospitalizations and ARI-associated hospitalizations as a hospital admission with a diagnosis code for influenza or an ARI, respectively (Supplemental Table 1). Follow-up data were available up to July 2017. To assess for possible bias in the study results, we included two negative control conditions: 1) all-cause injuries, and 2) skin and soft tissue infections (hereafter referred to as skin infections), using hospital diagnosis codes (Supplemental Table 1). This bias assessment was conducted to evaluate non-causal associations between prenatal exposure to seasonal IIV and the outcomes [20].

2.5. Covariate measurement

Maternal covariates included age at the time of her child's birth ($\leq$ 19, 20–24, 25–29, 30–34 and $\geq$ 35 years), Aboriginal status (Aboriginal, non-Aboriginal), socioeconomic status (quintiles between 1 (most disadvantaged) and 5 (least disadvantaged)), body mass index (BMI), parity (primiparous, one prior birth, $\geq$ 2 prior births), pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking during pregnancy, and gestational age at the first prenatal care visit. Child covariates included Aboriginal status, and season and year of birth. Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage, an area-based measure of relative access to resources for households within the same census collection district [21]. Preterm birth was categorized as: moderate to late preterm (32 to < 37 weeks gestation), very preterm (28 to < 32 weeks gestation), and extremely preterm (< 28 weeks gestation) birth. Small-for-gestational age birth was defined as birthweight < 10th percentile according to Australian national birthweight percentiles by sex and gestational age [22]. All covariates were selected *a priori* because they are known indicators of maternal influenza vaccination [23–28].

2.6. Statistical analyses

Descriptive statistics were calculated to compare demographic and health characteristics between vaccinated and unvaccinated mothers and their children. The odds of vaccination were estimated using univariate logistic regression models. To control for baseline probability of vaccination, we estimated inverse-probability of treatment weights using predicted probabilities derived from a multivariate logistic regression model including all maternal covariates. Standardized mean differences were calculated to assess the balance of maternal covariates between maternally vaccinated and unvaccinated children. Weighted Cox proportional hazard regression models were then used to estimate the hazard ratios (HRs) of study outcomes, comparing maternally vaccinated and unvaccinated children. Adjusted models additionally controlled for the child's Aboriginal status.

Time-at-risk commenced from birth and ended at the earliest of: a) the date the child reached five years of age, b) the last date of available data, c) the date the child died, or d) the date of event (Fig. 2). Children were able to contribute more than one event of interest. Unique episodes of care were considered those with $\geq$ 2 weeks between the date of separation and subsequent admission. A random effect term was incorporated in the model to account for multiple observations within individuals (i.e. more than one event per child). Sub-group analyses compared the risk of study outcomes by trimester of vaccination and specific age groups (< 6 months, 6 months to < 2 years, 2 to < 5 years, 6 months to < 5 years). To assess the potential impact of right truncation and exposure to differential exposure to influenza seasons, we performed a sensitivity analysis restricting to children born between 1 April 2012 and 30 September 2012 which coincides with the first seasonal influenza vaccine availability during the cohort period, fixes the child's age at each influenza season and allows for up to five years of follow-up. Additional sensitivity analyses included similar analyses with LCI restricted to children aged 6 to < 12 months and 1 to < 2 years as the time period where infant immunization would be least common [29]. All analyses were performed in STATA version 15.1 (StataCorp LLC, College Station, Texas, U.S.). Description of the detectable difference of risk of outcome measures between maternally vaccinated and unvaccinated children can be found in Supplemental Table 2.

3. Results

A total of 146,864 births were identified in WA during the study period. Of these, 22,103 (15.0%) records were excluded because the child was a non-singleton (n = 4,128), stillborn (n = 970), had missing covariate information (n = 16,570), or indeterminate vaccination status (n = 1,406). The final cohort included 124,760 singleton, live-born children from 106,206 mothers (Fig. 1). Maternal characteristics were balanced between maternally vaccinated and unvaccinated children (Table 1**;** Supplemental Fig. 1).

3.1. Maternal influenza vaccination

Of the 124,760 children, 14,396 (11.5%) were maternally vaccinated; 2,785 (19.4%) exposed during the first trimester, 5,558 (38.6%) during the second trimester, and 6,053 (42.1%) during the third trimester. The majority of mothers received influenza vaccine between March and July (n = 12,537; 87.1%). Vaccination was more common among primiparous women, women with pre-existing medical conditions and pregnancy complications, and non-smokers (Table 1). Women of the lowest socioeconomic status (odds ratio [OR]: 0.93; 95% confidence interval [CI]: 0.88–0.98) and mothers of preterm infants had lower odds of vaccination compared to term infants (OR: 0.91; 95% CI: 0.85, 0.98), and women who birthed during winter had the highest odds of being vaccinated as compared to summer (OR: 2.60; 95% CI: 2.46, 2.74).

3.2. Laboratory-confirmed influenza

There were 862 cases of LCI among 852 children aged < 5 years; 670 (77.7%) cases were influenza A virus (sub-type A/H1N1: 252

Table 1
Odds of vaccination by maternal and child characteristics of children born in Western Australia between 1 April 2012 and 1 July 2016 included in the study cohort.

Characteristic	Maternally unvaccinated (N = 110,364) n (%)	Maternally vaccinated (N = 14,396) n (%)	Unadjusted OR (95% CI)
Maternal characteristics			
Age (years):			
≤ 19	3,369 (3.1)	449 (3.1)	**1.13 (1.01–1.26)**
20–24	14,828 (13.4)	1,747 (12.1)	Reference
25–29	31,459 (28.5)	3,978 (27.6)	**1.07 (1.01–1.14)**
30–34	37,706 (34.2)	5,151 (35.8)	**1.16 (1.09–1.23)**
≥ 35	23,002 (20.8)	3,071 (21.3)	**1.13 (1.06–1.21)**
Aboriginal status:			
Aboriginal	5,296 (4.8)	717 (5.0)	1.04 (0.96–1.13)
Non-Aboriginal	105,068 (95.2)	13,679 (95.0)	Reference
Socioeconomic status:[a]			
Quintile 1 (most disadvantaged)	21,181 (19.2)	2,618 (18.2)	**0.93 (0.88–0.98)**
Quintile 2	22,674 (20.5)	3,019 (21.0)	1.00 (0.94–1.05)
Quintile 3	23,256 (21.1)	2,972 (20.6)	0.96 (0.91–1.01)
Quintile 4	22,217 (20.1)	2,979 (20.7)	1.00 (0.95–1.06)
Quintile 5 (least disadvantaged)	21,036 (19.1)	2,808 (19.5)	Reference
Body mass index:			
< 18.5 (underweight)	3,532 (3.2)	450 (3.1)	0.97 (0.87–1.07)
18.5 to < 25 (normal)	54,032 (49.0)	7,114 (49.4)	Reference
25 to < 30 (overweight)	30,720 (27.8)	3,875 (26.9)	0.96 (0.92–1.00)
≥ 30 (obese)	22,080 (20.0)	2,957 (20.5)	1.02 (0.97–1.06)
Parity:			
Primiparous	47,824 (43.3)	6,764 (47.0)	Reference
1 prior birth	38,216 (34.6)	4,958 (34.4)	**0.92 (0.88–0.95)**
≥ 2 prior births	24,324 (22.0)	2,674 (18.6)	**0.78 (0.74–0.81)**
Pre-existing medical conditions:			
Asthma	11,523 (10.4)	1,596 (11.1)	**1.07 (1.01–1.13)**
Essential hypertension	1,417 (1.3)	261 (1.8)	**1.42 (1.24–1.62)**
Pre-existing diabetes mellitus	916 (0.8)	191 (1.3)	**1.61 (1.37–1.88)**
Pregnancy complications:			
Gestational diabetes	11,310 (10.3)	1,688 (11.7)	**1.16 (1.10–1.23)**
Gestational hypertension	5,112 (4.6)	777 (5.4)	**1.17 (1.09–1.27)**
Pre-eclampsia	3,597 (3.3)	543 (3.8)	**1.16 (1.06–1.28)**
Smoked during pregnancy	10,540 (9.6)	1,269 (8.8)	**0.92 (0.86–0.97)**
Trimester of first prenatal care visit:			
First trimester	72,857 (66.0)	*	Reference
Second trimester	32,380 (29.3)	*	**0.82 (0.79–0.85)**
Third trimester	5,053 (4.6)	*	**0.54 (0.49–0.60)**
No prenatal care	74 (0.1)	<5	0.38 (0.14–1.05)
Year of birth:			
2012	19,930 (18.1)	1,304 (9.1)	Reference
2013	25,894 (23.5)	2,909 (20.2)	**1.72 (1.60–1.84)**
2014	26,345 (23.9)	3,205 (22.3)	**1.86 (1.74–1.99)**
2015	24,726 (22.4)	5,148 (35.8)	**3.18 (2.99–3.39)**
2016	13,469 (12.2)	1,830 (12.7)	**2.08 (1.93–2.24)**
Season of birth:			
Summer (Dec-Feb)	27,325 (24.8)	2,186 (15.2)	Reference
Autumn (Mar-May)	31,716 (28.7)	2,291 (15.9)	**0.90 (0.85–0.96)**
Winter (Jun-Aug)	26,062 (23.6)	5,413 (37.6)	**2.60 (2.46–2.74)**
Spring (Sep-Nov)	25,261 (22.9)	4,506 (31.3)	**2.23 (2.11–2.35)**
Child characteristics			
Sex:[b]			
Male	56,822 (51.5)	7,347 (51.0)	Reference
Female	53,539 (48.5)	7,049 (49.0)	1.02 (0.98–1.05)
Aboriginal status:			
Aboriginal	5,779 (5.2)	787 (5.5)	1.05 (0.97–1.13)
Non-Aboriginal	104,585 (94.8)	13,609 (94.5)	Reference
Birth outcomes:			
Preterm birth	7,390 (6.7)	887 (6.2)	**0.91 (0.85–0.98)**
Moderate-to-late preterm	6,587 (6.0)	819 (5.7)	0.95 (0.88–1.02)
Very preterm	520 (0.5)	52 (0.4)	0.76 (0.57–1.01)
Extremely preterm	283 (0.3)	16 (0.1)	**0.43 (0.26–0.71)**
Small-for-gestational age[c]	9,005 (8.2)	1,191 (8.3)	1.02 (0.95–1.08)

Abbreviations: OR, odds ratio; CI, confidence interval.
* In accordance with privacy and confidentiality guidelines by the DLB, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.
[a] Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) measure of relative socioeconomic advantage and disadvantage developed by the Australian Bureau of Statistics [21].
[b] The sex of < 5 maternally unvaccinated children was unknown.
[c] Small-for-gestational age was based on the Australian national birthweight percentiles by sex and gestational age, 1998–2007 [22].

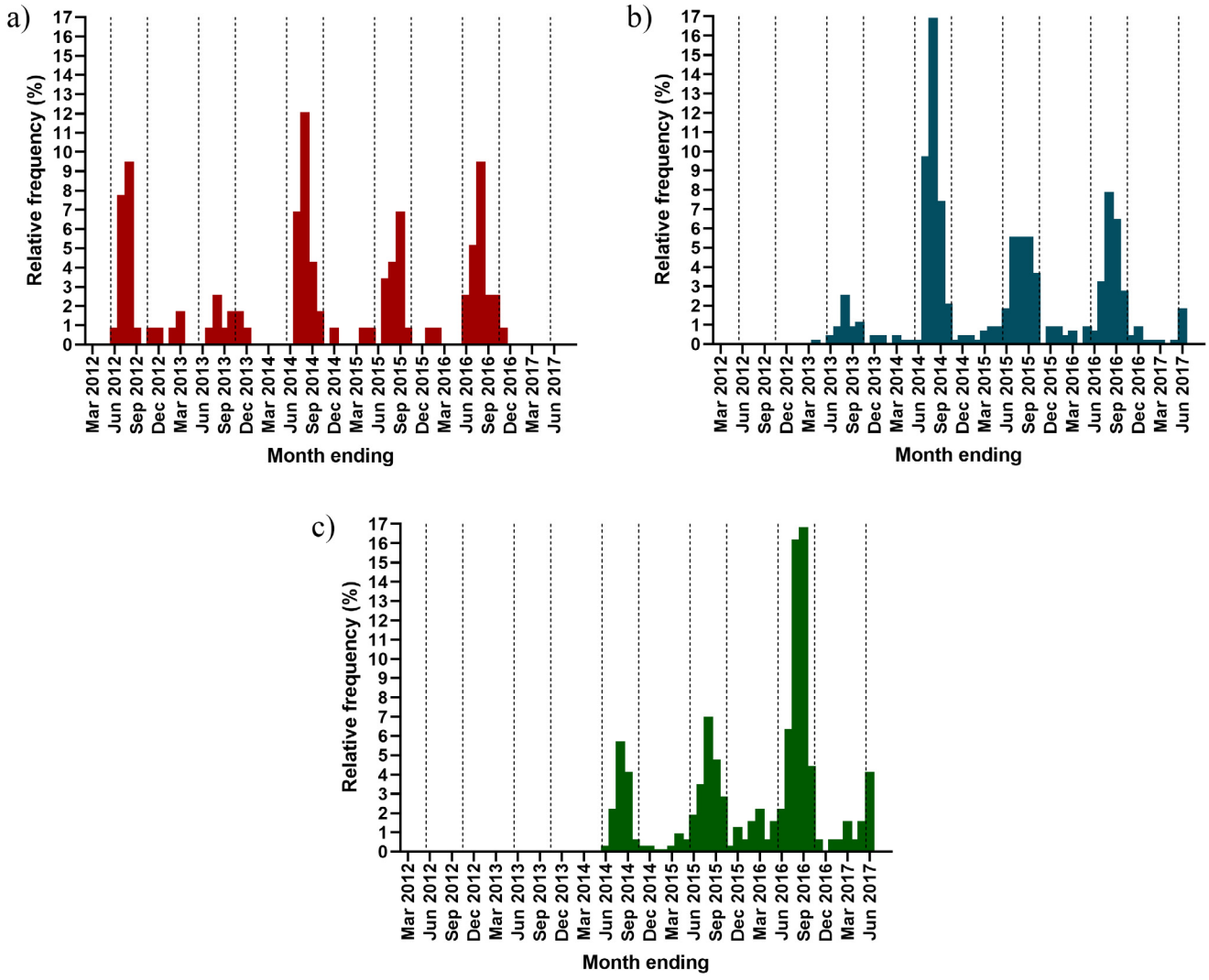

Fig. 3. Monthly rate of laboratory-confirmed influenza notifications, by age sub-group and month/year: a) children aged 0 to < 6 months, b) children aged 6 months to < 2 years, or c) children aged 2 to < 5 years—Western Australia, 1 April 2012–1 July 2017. Note: dashed lines indicate influenza seasons (Jun-Oct).

(29.2%); sub-type A/H3N2: 267 (31.0%); A/unsubtyped: 151 (17.5%)) and 192 (22.3%) were influenza B virus. One hundred and sixteen cases (13.5%) occurred in the first six months of life, 431 (50.0%) between 6 months and 2 years, and 315 (36.5%) between 2 and 5 years (Fig. 3). Two hundred and forty-three cases (28.2%) occurred among children born in 2012, 264 (30.6%) in 2013, 203 (23.5%) in 2014, 114 (13.2%) in 2015, and 38 (4.4%) in 2016.

We observed no difference in the risk of LCI between maternally vaccinated and maternally unvaccinated children from birth to 5 years of age (aHR: 1.10; 95% CI: 0.88, 1.38) (Table 2). Among infants aged < 6 months, we observed a lower risk of LCI associated with maternal influenza vaccination (aHR: 0.32; 95% CI: 0.12, 0.84) (Table 2). There were insufficient numbers to generate estimates by trimester of vaccination.

Among children aged 6 months to < 2 years, there was no difference in the risk of LCI between maternally vaccinated and maternally unvaccinated children (aHR: 1.33; 95% CI: 1.00, 1.76). However, an increased risk was observed among children of mothers vaccinated during the first trimester (aHR: 2.28: 95% CI: 1.41, 3.69). No associations were observed following maternal vaccination in later trimesters (Table 2). Sensitivity analyses restricting to children aged 6 to < 12 months (aHR: 2.70; 95% CI: 1.40, 5.98) and 1 to < 2 years (aHR: 2.00; 95% CI: 1.05, 3.80) similarly identified a higher risk of LCI following maternal vaccination during the first trimester (Supplemental Table 3). Among children aged 2 to < 5 years, no association was observed with maternal influenza vaccination (aHR: 1.14; 95% CI: 0.76, 1.71) (Table 2).

3.3. Influenza-associated hospitalization

A total of 360 influenza-associated hospitalizations were identified in 352 children aged < 5 years, of which 243 (67.5%) were associated with a LCI notification record. Similar to LCI, we observed no association between influenza-associated hospitalization and maternal influenza vaccination among children from birth to age 5 years (aHR: 0.91; 95% CI: 0.62, 1.33) (Table 3). Maternally vaccinated infants aged < 6 months had a lower risk of influenza-associated hospitalization compared to maternally unvaccinated infants (aHR: 0.38; 95% CI: 0.16, 0.91) (Table 3).

Among children aged 6 months to < 2 years and 2 to < 5 years, there was no difference in the risk of influenza-associated hospitalization between maternally vaccinated and maternally unvaccinated children (aHR: 1.09; 95% CI: 0.67, 1.78 and aHR: 1.40; 95% CI: 0.65, 3.01, respectively) (Table 3).

Table 2
Risk of laboratory-confirmed influenza infection associated with prenatal exposure to seasonal inactivated influenza vaccine among children < 5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged < 5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	759 (0.7)	93 (0.6)	28 (1.0)	34 (0.6)	31 (0.5)
Cases, n (%)	768 (0.7)	94 (0.7)	29 (1.0)	34 (0.6)	31 (0.5)
Unweighted HR (95% CI)	1 [Reference]	1.08 (0.87–1.35)	**1.71 (1.17–2.51)**	0.96 (0.68–1.35)	0.91 (0.63–1.30)
Weighted aHR (95% CI)[a]	1 [Reference]	1.10 (0.88–1.39)	**1.80 (1.21–2.68)**	0.97 (0.67–1.39)	0.91 (0.62–1.33)
Children aged < 6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	111 (0.1)	5 (0)	<5	<5	<5
Cases, n (%)	111 (0.1)	5 (0)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	**0.35 (0.14–0.85)**	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	**0.32 (0.12–0.84)**	-	-	-
Children aged 6 months to < 2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	368 (0.3)	61 (0.4)	19 (0.7)	23 (0.4)	19 (0.3)
Cases, n (%)	370 (0.3)	61 (0.4)	19 (0.7)	23 (0.4)	19 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.31 (1.00–1.72)	**2.13 (1.34–3.37)**	1.23 (0.81–1.88)	1.00 (0.63–1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	1.33 (1.00–1.76)	**2.28 (1.41–3.69)**	1.20 (0.78–1.86)	1.00 (0.61–1.64)
Children aged 2 to < 5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	284 (0.3)	28 (0.3)	8 (0.4)	11 (0.3)	9 (0.3)
Cases, n (%)	287 (0.3)	28 (0.3)	8 (0.4)	11 (0.3)	9 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.09 (0.74–1.60)	1.54 (0.76–3.11)	0.97 (0.53–1.78)	0.98 (0.51–1.91)
Weighted aHR (95% CI)[a]	1 [Reference]	1.14 (0.76–1.71)	1.52 (0.72–3.17)	1.05 (0.55–1.99)	1.04 (0.52–2.07)
Children aged 6 months to < 5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	648 (0.6)	88 (0.6)	26 (0.9)	34 (0.6)	28 (0.5)
Cases, n (%)	657 (0.6)	89 (0.6)	27 (1.0)	34 (0.6)	28 (0.5)
Unweighted HR (95% CI)	1 [Reference]	1.23 (0.98–1.54)	**1.91 (1.29–2.84)**	1.13 (0.80–1.60)	1.00 (0.68–1.46)
Weighted aHR (95% CI)[a]	1 [Reference]	1.24 (0.98–1.57)	**1.96 (1.29–2.97)**	1.13 (0.79–1.63)	1.01 (0.68–1.51)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; –, indeterminate (a stable estimate could not be generated due to the low number of outcomes).
Laboratory-confirmed influenza cases obtained from notification records reported to WANIDD.
[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

3.4. Acute respiratory infection-associated hospitalization

A total of 18,643 ARI-associated hospitalizations were identified in 13,638 children < 5 years of age, 5,394 in children aged < 6 months, 9,776 in children aged 6 months to < 2 years, and 3,495 in children aged 2 to < 5 years. The distribution of ARIs is presented in Supplemental Table 1.

There was no association between ARI-associated hospitalization and maternal influenza vaccination among children from birth to 5 years of age (aHR: 0.94; 95% CI: 0.88, 1.01) (Table 4). Maternally vaccinated infants aged < 6 months had a lower risk of an ARI-associated hospitalization compared to maternally unvaccinated infants (aHR: 0.85; 95% CI: 0.77, 0.94); maternal vaccination during the first and second trimester were associated with a lower risk of ARI-associated hospitalization (aHR: 0.67; 95% CI: 0.50, 0.88 and aHR: 0.79; 95% CI: 0.67, 0.93, respectively). This was not observed for maternal vaccination during the third trimester (aHR: 1.00; 95% CI: 0.87, 1.14). We observed no associations between maternal influenza vaccination and ARI-associated hospitalizations in other age groups (Table 4).

3.5. Bias assessment

There were 4,162 hospitalizations for all-cause injuries in 3,975 children and 1,687 hospitalizations for skin infections in 1,559 children aged < 5 years. We observed no difference in the risk of all-cause injury-hospitalization or skin infection-associated hospitalization between maternally vaccinated and maternally unvaccinated children from birth to 5 years of age by trimester of vaccination or age sub-group (Supplemental Table 4; Supplemental Table 5).

3.6. Sensitivity analysis

Of the 13,834 children born between 1 April 2012 and 30 September 2012, 789 (5.7%) were maternally vaccinated; 5 (0.6%) exposed during the first trimester, 315 (39.9%) during the second trimester, and 469 (59.4%) during the third trimester. We observed no difference in the risk of LCI or hospitalization for influenza, acute respiratory infections, all-cause injuries and skin infections between maternally vaccinated and maternally unvaccinated children aged < 5 years and 6 months to < 5 years (Supplemental Table 6).

4. Discussion

In this large, population-based cohort study of 124,760 children, we observed a lower risk of LCI, ARI-associated hospitalization, and influenza-associated hospitalization following seasonal IIV during pregnancy among infants aged < 6 months. No consistent differences in risks for children aged > 6 months were observed by maternal vaccination status. These findings suggest maternal vaccination is effective in preventing influenza in young infants, and

Table 3
Risk of influenza hospitalization associated with prenatal exposure to seasonal inactivated influenza vaccination among children < 5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged < 5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	318 (0.3)	34 (0.2)	7 (0.3)	12 (0.2)	15 (0.2)
Cases, n (%)	325 (0.3)	35 (0.2)	7 (0.3)	13 (0.2)	15 (0.2)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.63–1.28)	0.92 (0.43–1.95)	0.83 (0.46–1.50)	0.95 (0.56–1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.62–1.33)	1.29 (0.58–2.85)	0.80 (0.43–1.48)	0.85 (0.49–1.47)
Children aged < 6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	106 (0.1)	6 (0)	<5	<5	5 (0.1)
Cases, n (%)	108 (0.1)	6 (0)	<5	<5	5 (0.1)
Unweighted HR (95% CI)	1 [Reference]	**0.43 (0.19–0.97)**	-	-	0.84 (0.34–2.07)
Weighted aHR (95% CI)[a]	1 [Reference]	**0.38 (0.16–0.91)**	-	-	0.68 (0.26–1.73)
Children aged 6 months to < 2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	145 (0.1)	20 (0.1)	<5	10 (0.2)	8 (0.1)
Cases, n (%)	146 (0.1)	21 (0.1)	<5	11 (0.2)	8 (0.1)
Unweighted HR (95% CI)	1 [Reference]	1.13 (0.70–1.82)	-	1.49 (0.77–2.89)	1.05 (0.52–2.15)
Weighted aHR (95% CI)[a]	1 [Reference]	1.09 (0.67–1.78)	-	1.36 (0.70–2.65)	0.96 (0.47–1.99)
Children aged 2 to < 5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	69 (0.1)	8 (0.1)	<5	<5	<5
Cases, n (%)	71 (0.1)	8 (0.1)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	1.23 (0.59–2.56)	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	1.40 (0.65–3.01)	-	-	-
Children aged 6 months to < 5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	212 (0.2)	28 (0.2)	6 (0.2)	12 (0.2)	10 (0.2)
Cases, n (%)	217 (0.2)	29 (0.2)	6 (0.2)	13 (0.2)	10 (0.2)
Unweighted HR (95% CI)	1 [Reference]	1.16 (0.78–1.73)	1.23 (0.54–2.78)	1.26 (0.69–2.30)	1.01 (0.54–1.91)
Weighted aHR (95% CI)[a]	1 [Reference]	1.18 (0.77–1.80)	1.67 (0.69–4.01)	1.20 (0.64–2.23)	0.94 (0.48–1.83)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).
Influenza-associated hospitalization obtained from ICD-10-AM codes: J09-J11, found in the principal and additional diagnosis fields of hospital inpatient records (Supplemental Table 1).
[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

does not impact the susceptibility to respiratory infections through early childhood.

We did observe a two-fold increase in the risk of LCI associated with maternal influenza vaccination when administered during the first trimester of pregnancy. The first six months of life is an important window for priming the immune system, and the influence of maternal immunization beyond passive immunity is not well-understood [30]. The presence of maternal antibodies from other maternal vaccines has been shown to inhibit the development of children's primary antibody response [31], including blunted response to pertussis, *Haemophilus influenzae B* and pneumococcal vaccines [32]. It is not currently known whether this is also the case with seasonal influenza vaccines. It is possible that although maternally vaccinated infants are protected by maternal antibodies early in life, once these antibodies wane around 2–3 months after birth, this may leave a temporary window of susceptibility [30]. This may explain the temporary increased risk of LCI infection among children aged 6 months to < 2 years whose mothers were vaccinated in first trimester. A Danish cohort of children whose mothers received pandemic influenza vaccine during the first trimester of pregnancy observed down-regulation of key immune mediators in airway mucosal cells, suggesting a compromised local immune defence [33]. This effect was enhanced the earlier in the pregnancy the mothers received vaccination. While this down-regulation was observed in neonates and the study was not powered to examine the immune response later in infancy, it may be hypothesized that the boosted adaptive immune response in vaccinated mothers was responsible for down-regulation of the fetal immune system in this study. Whether this down-regulation is temporary, has lasting effects, or is also the case with seasonal vaccines is unknown and requires further examination.

Despite this, there are other explanations for these results, and this finding requires further evaluation. First, sensitivity analyses restricting the influence of truncation and exposure to different influenza seasons did not suggest an increased risk of LCI for children 6 months to < 5 years of age. However, our cohort was too small to perform analyses specific to first trimester exposure. Second, we were unable to measure receipt of influenza vaccines during childhood in this cohort and it is possible that vaccination rates in maternally vaccinated children varied to rates in maternally unvaccinated children [34]; however, sensitivity analyses restricted to the time period when childhood influenza vaccination is unlikely showed similar results, suggesting this was not a strong factor in our results. Another possibility is that residual confounding influenced our results. Although we did not identify associations in our negative control analysis, and we attempted to restrict the influence of health-seeking behavior using inverse-probability treatment weighting, we cannot entirely exclude the possible influence of confounding in our results.

The main strengths of our study include the availability of a large, population-based birth cohort and the use of record linkage to incorporate detailed information on birth, perinatal, and health

Table 4
Risk of acute respiratory infection hospitalization associated with prenatal exposure to seasonal inactivated influenza vaccination among children < 5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged < 5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	12,193 (11.0)	1,445 (10.0)	255 (9.2)	579 (10.4)	611 (10.1)
Cases, n (%)	16,706 (15.1)	1,937 (13.5)	356 (12.8)	785 (14.1)	796 (13.2)
Unweighted HR (95% CI)	1 [Reference]	0.96 (0.90–1.02)	0.90 (0.78–1.04)	0.96 (0.87–1.06)	0.97 (0.89–1.07)
Weighted aHR (95% CI)[a]	1 [Reference]	0.94 (0.88–1.01)	0.88 (0.75–1.02)	0.97 (0.87–1.07)	0.95 (0.86–1.05)
Children aged < 6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	4,434 (4.0)	506 (3.5)	70 (2.5)	180 (3.2)	256 (4.2)
Cases, n (%)	4,838 (4.4)	556 (3.9)	83 (3.0)	193 (3.5)	280 (4.6)
Unweighted HR (95% CI)	1 [Reference]	**0.88 (0.80–0.97)**	**0.68 (0.53–0.88)**	**0.79 (0.68–0.92)**	1.05 (0.93–1.20)
Weighted aHR (95% CI)[a]	1 [Reference]	**0.85 (0.77–0.94)**	**0.67 (0.50–0.88)**	**0.79 (0.67–0.93)**	1.00 (0.87–1.14)
Children aged 6 months to < 2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	6,775 (6.2)	842 (5.9)	170 (6.1)	351 (6.3)	321 (5.3)
Cases, n (%)	8,702 (7.9)	1,074 (7.5)	218 (7.8)	446 (8.0)	410 (6.8)
Unweighted HR (95% CI)	1 [Reference]	0.97 (0.89–1.05)	1.02 (0.86–1.21)	1.00 (0.89–1.13)	0.91 (0.80–1.03)
Weighted aHR (95% CI)[a]	1 [Reference]	0.97 (0.90–1.06)	0.99 (0.83–1.18)	1.03 (0.91–1.16)	0.91 (0.80–1.04)
Children aged 2 to < 5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	2,570 (3.0)	252 (2.8)	46 (2.5)	116 (3.3)	90 (2.6)
Cases, n (%)	3,186 (3.7)	309 (3.5)	56 (3.0)	147 (4.1)	106 (3.0)
Unweighted HR (95% CI)	1 [Reference]	1.06 (0.92–1.22)	0.93 (0.68–1.29)	1.13 (0.92–1.39)	1.03 (0.83–1.29)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.87–1.17)	0.90 (0.65–1.24)	1.06 (0.85–1.32)	1.01 (0.80–1.27)
Children aged 6 months to < 5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	8,678 (7.9)	1,028 (7.2)	199 (7.2)	437 (7.9)	392 (6.5)
Cases, n (%)	11,883 (10.8)	1,383 (9.6)	274 (9.9)	593 (10.7)	516 (8.5)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.92–1.07)	1.00 (0.85–1.18)	1.03 (0.92–1.16)	0.93 (0.83–1.05)
Weighted aHR (95% CI)[a]	1 [Reference]	0.98 (0.91–1.06)	0.97 (0.82–1.14)	1.04 (0.92–1.16)	0.93 (0.83–1.05)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).
Acute respiratory infection-associated hospitalization obtained from ICD-10-AM codes: B34, J05, J06, J09-J11, J12-J18, J20, J21, J22, found in the principal and additional diagnosis fields of hospital inpatient records (Supplemental Table 1).
[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

care information. With the exception of antenatal vaccination registers, these registers are nationally mandated and provide data to the Australian Institute of Health and Welfare, and the quality is considered to be high [35]. Record linkage has been well established in WA since 1995 [36]. The MNS is also estimated to capture 99% of all births in WA [16]. Furthermore, through the use of WANIDD data, we were able to assess laboratory-confirmed outcomes with high specificity [37], rather than influenza identified through diagnostic codes alone which have been shown to under-report the incidence of influenza admissions [38].

The study had some limitations: firstly, the inability to measure childhood influenza vaccination, which is a potential confounder and effect modifier. Despite this, childhood influenza vaccine coverage was low (< 10%) during our study period [29], indicating this was unlikely to have significantly influenced our results. It is possible that childhood vaccination is associated with maternal vaccination, and if this is the case, our analyses accounting for confounding maternal factors may have by proxy adjusted for some influence of childhood vaccination as a confounder. Secondly, maternal vaccination status was captured by medical reports from immunization providers. Although the immunizations identified by this system are likely to reflect accurate medical information, it is possible that immunization capture was incomplete [17]. Thirdly, the use of LCI as an endpoint is a strength of our study, however, there may be some outcome misclassification, in cases where a child was not tested for influenza. For this reason, we included additional endpoints considering diagnostic coding. Finally, despite the large cohort size in our study, some outcomes were suppressed when stratifying by trimester of vaccination due to < 5 cases, and post-hoc power analysis suggests some associations may not have been detected.

5. Conclusion

Few studies have evaluated the effects of seasonal IIV during pregnancy on acute respiratory infectious outcomes beyond infancy and into early childhood. As maternal vaccination programs continue to expand globally, it will become increasingly important to understand the comprehensive impact of prenatal exposure to vaccines on child health, particularly the immune signature of the child [39]. Overall, our findings suggest maternal influenza vaccination prevented influenza in young infants aged < 6 months and was not associated with long-term differences in the risk of acute respiratory infections among children aged < 5 years. However, there was a suggested increase in the risk of LCI among children aged 6 months to < 2 years following maternal influenza vaccination during the first trimester. This observed association could be due to residual confounding, differential exposure to influenza seasons, and/or the absence of vaccination information beyond six months of age implying that these results should be interpreted cautiously. Regardless, we believe our results

support current vaccine policies and practices prioritizing influenza immunization during pregnancy to protect young infants from influenza infection, and suggests the need for additional studies to further evaluate longer term health outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

D.F., M.S., and A.K.R. performed all data management. D.F. performed all analysis and led the writing of the first draft of the manuscript. A.K.R., M.S., G.P., and H.C.M. contributed to the study design, interpretation of data and writing of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.11.084.

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