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Seasonal Influenza Vaccination During Pregnancy and the Risk of Major Congenital Malformations in Live-born Infants: A 2010–2016 Historical Cohort Study

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Background. Available evidence indicates that seasonal inactivated influenza vaccination during pregnancy protects both the mother and her newborn and is safe. Nevertheless, ongoing safety assessments are important in sustaining vaccine uptake. Few studies have explored safety in relation to major congenital malformations (MCMs), particularly in the first trimester when most organogenesis occurs.

Methods. Anonymized UK primary care data (the Clinical Practice Research Datalink), including a recently developed Pregnancy Register, were used to identify live-born singletons delivered between 2010 and 2016. Maternal influenza vaccination was determined using primary care records and stratified by trimester. Ascertainment of MCMs from infant primary care records was maximized by linkage to hospitalization data and death certificates. The relationship between vaccination and MCMs recorded in the year after delivery and in early childhood was then assessed using multivariable Cox regression.

Results. A total of 78 150 live-birth pregnancies were identified: 6872 (8.8%) were vaccinated in the first trimester, 11 678 (14.9%) in the second, and 12 931 (16.5%) in the third. Overall, 5707 live births resulted in an infant with an MCM recorded in the year after delivery and the adjusted hazard ratio when comparing first-trimester vaccination to no vaccination was 1.06 (99% CI, .94–1.19; $P = .2$). Results were similar for second- and third-trimester vaccination and for analyses considering MCMs recorded beyond the first birthday.

Conclusions. In this large, population-based historical cohort study there was no evidence to suggest that seasonal influenza vaccine was associated with MCMs when given in the first trimester or subsequently in pregnancy.

Keywords. pregnancy; influenza vaccine; safety; congenital malformations.

Influenza vaccination during pregnancy provides protection from influenza-related complications in mothers and newborn infants but women are often concerned about their infant's safety [1–6]. Postlicensure studies, most of which only examined the 2009/2010 pandemic influenza vaccine, have not demonstrated an association between maternal influenza vaccination and major congenital malformations (MCMs) (pooled odds ratio, 1.03; 95% confidence interval [CI], .7–1.6; $P = .38$; n = 20 studies) [7–11].

A small number of studies have examined seasonal influenza vaccines (SIVs) using data from the United States or Canada and have not found evidence of an increased risk of MCMs [12–16]. However, all but one [16] were limited by low numbers of vaccinations in the first trimester, the critical period of organogenesis when the risk of MCMs is highest [12–15]. Furthermore, although MCMs continue to be diagnosed and recorded into early childhood [17–19], most studies ended follow-up of infants shortly after delivery [13–15].

We examined the association between SIV and MCMs in a different setting using a large UK cohort. Analyses were stratified by trimester of vaccination and the ascertainment of MCMs was maximized through long-term follow-up of infants and the use of linked primary care, hospitalization, and mortality datasets.

METHODS

Data Sources

This study utilized the Clinical Practice Research Datalink (CPRD), the CPRD/London School of Hygiene and Tropical

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Medicine (LSHTM) Pregnancy Register, hospital admissions data from the Hospital Episode Statistics database (HES), Office for National Statistics (ONS) death certificate data, deprivation quintiles linked to household postcodes, and data on influenza activity from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre.

The CPRD contains anonymized, electronic primary care records for 7% of the UK population registered at a general practice. It includes diagnoses and procedures recorded using the Read codes (version 2) hierarchical clinical coding system [20, 21], vaccination records, and prescriptions [22]. The CPRD has been shown to be broadly representative of the UK population and diagnostic validity is high [22, 23].

The Pregnancy Register lists all pregnancies identified in the CPRD for women aged 11–49 years [24]. It includes pregnancy outcomes and estimates of pregnancy timings derived from all available pregnancy data in CPRD including estimated delivery dates, last menstrual period dates, ultrasound dating scans, and prematurity records. The first, second, and third trimesters are defined as the pregnancy start through week 13, week 14 through 26, and week 27 through the pregnancy end, respectively. Live-birth deliveries are linked to records of infants registered at the same practice as their mother. Validation of the Pregnancy Register against linked electronic maternity records in HES has indicated overall good agreement, suggesting most pregnancies are well captured in the register [24].

Patient data in CPRD can be linked to the HES and ONS data for 75% of English practices [22]. Linked HES data include information on diagnoses and procedures, recorded using the *International Classification of Diseases, 10th revision* (ICD-10), and the Classification of Surgical Operations and Procedures (OPCS-4), respectively. The ONS death certificate data include primary and contributory causes of death recorded using ICD-10. Deprivation quintiles are derived from the 2015 Index of Multiple Deprivation (IMD) for Lower Super Output Areas [25].

Weekly general practice consultation rates for influenza-like illness from the RCGP were used to identify periods of influenza circulation above baseline levels for each season. The validity of these data has been confirmed through microbiological surveillance [26].

This study received approval from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17_040RA); the approved protocol was made available to the reviewers. Approval was also received from LSHTM's ethics committee (reference 13720).

Study Design

This historical cohort study compared live-birth pregnancies in women who received SIV, stratified by trimester of vaccination, with those who were unvaccinated. The primary outcome was the presence of any MCMs among infants in the year after delivery. Secondary outcomes examined any MCMs, major limb malformations, and congenital heart defects recorded after delivery and anytime in the study period between 1 September 2010 and 31 March 2016 (the latest date for which all linked data were available).

Study Population

Pregnancies resulting in a live-born singleton during the study period were identified from the Pregnancy Register. Pregnant women had to be registered at an up-to-standard practice (a quality standard set by CPRD to indicate continuous recording of data within the practice) [22] for at least 6 months before the start of pregnancy to enable the ascertainment of preconception exposures. Live-born infants had to be eligible for HES and ONS linkage. Finally, pregnancies were required to overlap with a period of influenza vaccine availability (1 September to 31 March, annually) by at least 1 week.

Identifying Vaccinations

In the United Kingdom, pregnant women are offered SIV in any trimester [27]. The earliest vaccination record in each influenza season was identified in CPRD from immunization records, prescriptions, or Read codes, and used to determine the trimester of vaccination. Pregnancies were excluded if the timing or nature of vaccination was uncertain (eg, if there was a possibility that SIV was received outside of the practice at an unknown time or a possibility that pandemic vaccine was received) (Figure 1).

Identifying Major Congenital Malformations

Code lists for MCMs were developed with a consultant neonatologist (S. T. K.), following EUROCAT guidelines (see Supplementary Material; code lists are available at https://datacompass.lshtm.ac.uk/1629/) [28]. Major congenital malformations were then ascertained from infant records in CPRD, HES data for diagnoses and procedures, and ONS. Pregnancies were excluded if there was an antenatal or infant record indicating a chromosomal or heritable anomaly, a malformation due to a known teratogen (eg, fetal alcohol syndrome), or a congenital infection associated with malformations. Infants were followed up from delivery for 1 year or until the end of the study period. Follow-up ended earlier if they died, left the practice, or the practice stopped collecting data for CPRD.

Potential Confounders

We considered a priori confounders to be maternal age and ethnicity, geographical region (due to variation in vaccine uptake and MCM ascertainment), and influenza season. Other potential confounders included the following: household deprivation quintile (IMD), number of children in the household, maternal smoking, hazardous drinking, extreme body mass index (BMI) of less than 18 kg/m^2 or 35 kg/m^2 or higher, belonging to

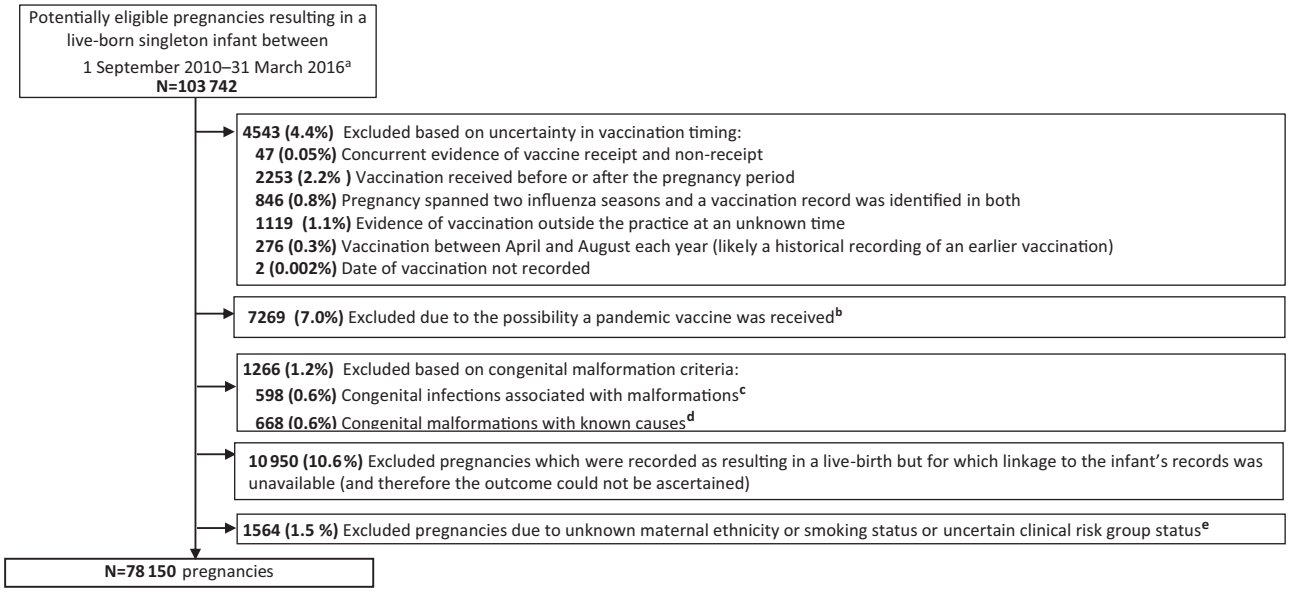

Figure 1. Derivation of pregnancies used in analyses. [a]At least 1 week of the pregnancy had to occur when influenza vaccine was available. All infants had to be eligible for linkage to HES and ONS data. [b]Pandemic vaccine was available alongside SIV in 2009/2010 and 2010/2011. Pregnant women could be offered the pandemic vaccine in 2010/2011 or in 2009/2010 if their pregnancy ended after 1 September 2010 but started in the prior influenza season. Pregnant women who received pandemic vaccine or an unspecified influenza vaccine in 2009/2010 or 2010/2011 were excluded. [c]Toxoplasmosis, rubella, cytomegalovirus, herpes, parvovirus, varicella-zoster, syphillis, HIV. [d]Chromosomal anomalies, heritable conditions, or malformations due to a known teratogen. [e]Among pregnancies for which linkage to the infant record was available, 720 had unknown maternal ethnicity, 403 had unknown maternal smoking status, and 449 had an uncertain maternal clinical risk group status. Abbreviations: HES, Hospital Episode Statistics database, HIV, human immunodeficiency virus; ONS, Office for National Statistics; SIV, seasonal influenza vaccine.

another clinical risk group for which vaccination was recommended during the study period [27], non–pregnancy-related chronic hypertension, exposure to teratogenic drugs or live vaccines, and number of weeks the first trimester overlapped with influenza activity above baseline levels (see Supplementary Table 1 for details of how these were derived).

Statistical Analyses

Baseline pregnancy characteristics were described by vaccination status. Logistic regression was used initially to model the univariable relationship between vaccination and MCMs recorded in the year after delivery and assess confounding. After a priori confounders, remaining potential confounders were added individually to the logistic regression model and assessed for a 5% or greater change in the odds ratios between first-trimester vaccination or vaccination anytime and MCMs. Multicollinearity was monitored between IMD, ethnicity, and region and between the number of children in the household and maternal age. Finally, random-effects models were used to assess clustering by mother and practice. Once confounders had been identified using logistic regression models, all final analyses were conducted using Cox proportional hazards models to account for improved ascertainment of the outcome among infants with longer follow-up time. Results were compared with those from logistic regression. To account for multiple analyses, 99% CIs were calculated. All models were complete case analyses. We estimated we had more than 90% power to detect a risk ratio of 1.2 in primary analyses.

Three sensitivity analyses were conducted. First, we included pregnancies in women who received SIV in the 4 weeks prior to their start to account for any imprecision in the estimated pregnancy start dates. Second, we included MCMs recorded in HES or ONS after follow-up in CPRD had ended because the infant left the practice or the practice ended data collection. In the main analyses, pregnancies of women with unknown BMI or a BMI between 18 and 34 kg/m^2 were combined in a single category as they had comparable associations with MCMs. The third sensitivity analysis excluded pregnancies of women with unknown BMI. STATA version 14.2 (StataCorp) was used for all analyses.

RESULTS

Characteristics of the Eligible Study Cohort

We identified 103 742 potentially eligible pregnancies resulting in live-born singletons during the study period. After exclusions were applied, the final cohort included 78 150 pregnancies among 71 124 women (Figure 1). Most pregnancies were in white women (85.5%) aged 25–34 (58.9%) years (Table 1).

Vaccine uptake was 40.3% (n = 31 481): 8.8% (n = 6872) in the first trimester, 14.9% (n = 11 678) in the second trimester, and 16.5% (n = 12 931) in the third trimester. Vaccination in the first trimester or anytime in pregnancy was less likely if the woman was young, of Black ethnicity, living in a more deprived

Table 1. Characteristics of Eligible Pregnancies Included in Analyses, by Vaccination Status

	No. of Pregnancies (%) (N = 78 150)	No. of Pregnancies Unvaccinated (%) (n = 46 669)	No. of Pregnancies Vaccinated in Trimester 1 (%) (n = 6872)	No. of Pregnancies Vaccinated Anytime (%) (n = 31 481)
Maternal age (years)				
<18	719 (0.9)	458 (63.7)	33 (4.6)	261 (36.3)
18–24	13 243 (17)	8451 (63.8)	982 (7.4)	4792 (36.2)
25–34	46 030 (58.9)	27 138 (59)	4150 (9)	18 892 (41)
≥35	18 158 (23.2)	10 622 (58.5)	1707 (9.4)	7536 (41.5)
Maternal ethnicity				
White	66 849 (85.5)	39 618 (59.3)	5939 (8.9)	27 231 (40.7)
South Asian	5501 (7)	3272 (59.5)	507 (9.2)	2229 (40.5)
Black	2881 (3.7)	1953 (67.8)	196 (6.8)	928 (32.2)
Other	1850 (2.4)	1171 (63.3)	146 (7.9)	679 (36.7)
Mixed	1069 (1.4)	655 (61.3)	84 (7.9)	414 (38.7)
Maternal IMD status[a]				
1 = least deprived	15 847 (20.3)	8730 (55.1)	1579 (10)	7117 (44.9)
2	14 905 (19.1)	8569 (57.5)	1345 (9)	6336 (42.5)
3	15 144 (19.4)	8880 (58.6)	1406 (9.3)	6264 (41.4)
4	16 064 (20.6)	10 015 (62.3)	1304 (8.1)	6049 (37.7)
5 = most deprived	16 190 (20.7)	10 475 (64.7)	1238 (7.7)	5715 (35.3)
Region				
London	12 922 (16.5)	8295 (64.2)	991 (7.7)	4627 (35.8)
North East	1811 (2.3)	1203 (66.4)	113 (6.2)	608 (33.6)
North West	11 636 (14.9)	6771 (58.2)	1133 (9.7)	4865 (41.8)
Yorkshire and The Humber	1453 (1.9)	922 (63.5)	123 (8.5)	531 (36.6)
East Midlands	780 (1)	549 (70.4)	45 (5.8)	231 (29.6)
West Midlands	8545 (10.9)	4561 (53.4)	997 (11.7)	3984 (46.6)
East of England	7862 (10.1)	4463 (56.8)	741 (9.4)	3399 (43.2)
South West	9974 (12.8)	5936 (59.5)	777 (7.8)	4038 (40.5)
South Central	11 670 (14.9)	6710 (57.5)	1157 (9.9)	4960 (42.5)
South East Coast	11 497 (14.7)	7259 (63.1)	795 (6.9)	4238 (36.9)
Mother was part of a clinical risk group[b]				
No	73 804 (94.4)	44 513 (60.3)	6230 (8.4)	29 291 (39.7)
Yes	4346 (5.6)	2156 (49.6)	642 (14.8)	2190 (50.4)
Maternal smoking status				
Nonsmoker	41 081 (52.6)	23 922 (58.2)	3729 (9.1)	17 159 (41.8)
Current smoker	17 687 (22.6)	11 630 (65.8)	1278 (7.2)	6057 (34.3)
Ex-smoker	19 382 (24.8)	11 117 (57.4)	1865 (9.6)	8265 (42.6)
Maternal hazardous drinking				
No	77 502 (99.2)	46 308 (59.8)	6811 (8.8)	31 194 (40.3)
Yes	648 (0.8)	361 (55.7)	61 (9.4)	287 (44.3)
Extreme maternal BMI				
No	71 335 (91.3)	42 560 (59.7)	6235 (8.7)	28 775 (40.3)
Underweight (<18 kg/m^2)	1656 (2.1)	1042 (62.9)	147 (8.9)	614 (37.1)
Obese (≥35 kg/m^2)	5159 (6.6)	3067 (59.5)	490 (9.5)	2092 (40.6)
Maternal chronic hypertension (nonpregnancy related)				
No	77 097 (98.7)	46 074 (59.8)	6760 (8.8)	31 023 (40.2)
Yes	1053 (1.4)	595 (56.5)	112 (10.6)	458 (43.5)
Maternal exposure to teratogenic medication(s)[c] or live vaccines[d]				
No	73 370 (93.9)	43 928 (59.9)	6386 (8.7)	29 442 (40.1)
Yes	4780 (6.1)	2741 (57.3)	486 (10.2)	2039 (42.7)
Influenza season				
2009/2010	5234 (6.7)	5171 (98.8)	0 (0)	63 (1.2)
2010/2011	13 040 (16.7)	10 135 (77.7)	425 (3.3)	2905 (22.3)
2011/2012	18 468 (23.6)	11 254 (60.9)	1607 (8.7)	7214 (39.1)
2012/2013	15 910 (20.4)	7833 (49.2)	2067 (13)	8077 (50.8)
2013/2014	13 383 (17.1)	6906 (51.6)	1503 (11.2)	6477 (48.4)
2014/2015	9987 (12.8)	4715 (47.2)	1251 (12.5)	5272 (52.8)
2015/2016	2128 (2.7)	655 (30.8)	19 (0.9)	1473 (69.2)

Table 1. Continued

	No. of Pregnancies (%) (N = 78 150)	No. of Pregnancies Unvaccinated (%) (n = 46 669)	No. of Pregnancies Vaccinated in Trimester 1 (%) (n = 6872)	No. of Pregnancies Vaccinated Anytime (%) (n = 31 481)
No. of weeks the first trimester overlapped with influenza activity above baseline levels				
None	63 145 (80.8)	35 467 (56.2)	4813 (7.6)	27 678 (43.8)
0–2	6556 (8.4)	4649 (70.9)	1091 (16.6)	1907 (29.1)
2–4	1668 (2.1)	1200 (71.9)	154 (9.2)	468 (28.1)
4–6	2059 (2.6)	1525 (74.1)	260 (12.6)	534 (25.9)
6–8	2954 (3.8)	2377 (80.5)	346 (11.7)	577 (19.5)
8–10	703 (0.9)	541 (77)	88 (12.5)	162 (23)
10–12	1065 (1.4)	910 (85.5)	120 (11.3)	155 (14.6)
No. of children in the maternal household				
None	27 868 (35.7)	15 211 (54.6)	2833 (10.2)	12 657 (45.4)
1–2	42 911 (54.9)	26 419 (61.6)	3565 (8.3)	16 492 (38.4)
≥3	7371 (9.4)	5039 (68.4)	474 (6.4)	2332 (31.6)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.

[a]For 46 (0.06%) pregnancies, maternal household IMD was unavailable and practice-level IMD was used.

[b]Chronic respiratory, heart, kidney, liver or neurological disease; diabetes; immunosuppression due to disease or treatment; asplenia or dysfunction of the spleen.

[c]Exposure from 6 months before pregnancy start until the end of the first trimester.

[d]Exposure from 3 months before pregnancy start until the end of the first trimester.

area, not part of a clinical risk group for which vaccination was recommended [27], unexposed to teratogenic medications and/or live vaccines, a current smoker, or part of a household with children (Table 1, Supplementary Table 2). Vaccination also varied by region and influenza season.

Of the 78 150 pregnancies, 7.3% (n = 5707) resulted in an infant with an MCM recorded in the year after delivery, while 7.7% (n = 6029) had an MCM recorded after delivery and anytime in the study period. Most MCMs were recorded early in life, with 51% recorded at delivery and 87.2% in the following 3 months (Supplementary Figure 1). Most infants had at least 1 year of follow-up (73.5%) and almost half had at least 2 years of follow-up (48.9%) (Supplementary Table 3).

Primary Analyses

The univariable Cox regression analysis suggested an increased rate of MCMs recorded in the year after delivery among those vaccinated anytime in pregnancy compared with those never vaccinated (hazard ratio [HR], 1.10; 99% CI, 1.03–1.18; $P < .001$). Results were similar for first-trimester and second-trimester vaccination (Table 2). However, all associations were eliminated following adjustment for a priori confounders: maternal age, ethnicity, region, and influenza season (Table 2). The most important of these appeared to be region and season; HRs remained similar upon the addition of age and ethnicity (Supplementary Tables 4 and 5). Both region and season were associated with age and ethnicity (χ^2, $P < .001$), suggesting that

Table 2. Examining the Association Between Vaccination and Major Congenital Malformations

Time of Vaccination During Pregnancy (No. of Pregnancies)	No. MCMs/Person-years (Rate per 100 Person-years)	HR, Unadjusted (99% CI)	*P*	HR, Adjusted for A Priori Confounders (99% CI)	*P*	HR, Adjusted for All Potential Confounders (99% CI)	*P*
Models including MCMs ascertained in the year after delivery (N = 5707 MCMs)							
Never (46 669)	3289/38 898 (8.5)	1.00		1.00		1.00	
Any trimester (31 481)	2418/24 827 (9.7)	1.10 (1.03–1.18)	<.001	1.03 (.96–1.11)	.33	1.02 (.94–1.10)	.54
Trimester 1 (6872)	565/5560 (10.2)	1.17 (1.04–1.32)	<.001	1.08 (.96–1.22)	.11	1.06 (.94–1.19)	.23
Trimester 2 (11 678)	902/9153 (9.9)	1.11 (1.01–1.22)	.006	1.03 (.93–1.14)	.45	1.02 (.92–1.13)	.63
Trimester 3 (12 931)	951/10 115 (9.4)	1.05 (.96–1.16)	.17	1.00 (.91–1.10)	>.99	.99 (.90–1.10)	.86
Models including MCMs ascertained after delivery and anytime in the study period (N = 6029 MCMs)							
Never (46 669)	3505/102 311 (3.4)	1.00		1.00		1.00	
Any trimester (31 481)	2524/54 389 (4.6)	1.09 (1.02–1.17)	.001	1.03 (.96–1.10)	.36	1.02 (.94–1.09)	.56
Trimester 1 (6872)	594/11 648 (5.1)	1.18 (1.05–1.32)	<.001	1.09 (.97–1.22)	.07	1.07 (.95–1.20)	.16
Trimester 2 (11 678)	941/20 203 (4.7)	1.10 (1.00–1.21)	.008	1.03 (.93–1.13)	.48	1.02 (.92–1.13)	.65
Trimester 3 (12 931)	989/22 539 (4.4)	1.04 (.95–1.14)	.27	.99 (.90–1.09)	.85	.99 (.90–1.09)	.73

A priori confounders were maternal age, maternal ethnicity, region, and influenza season. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension, and exposure to teratogenic drugs and/or live vaccines.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; IMD, Index of Multiple Deprivation; MCM, major congenital malformation.

adjustment for the former likely resulted in partial adjustment for the latter.

Of the remaining potential confounders, only maternal IMD and number of children in the household were associated with both vaccination and MCMs in univariable analyses (Supplementary Tables 2 and 6). However, upon addition to the model, neither these nor any others altered HRs by 5% or more (Supplementary Tables 4 and 5). Fully adjusted models showed no evidence of an association between vaccination anytime (HR, 1.02; 99% CI, .94–1.10; $P = .54$), vaccination in the first trimester (HR, 1.06; 99% CI, .94–1.19; $P = .23$), or vaccination in the second trimester (HR, 1.02; 99% CI, .92–1.13; $P = .63$) and MCMs recorded in the year after delivery (Table 2). The logistic regression models used to investigate confounding gave very similar results to our final Cox regression models (Supplementary Tables 4 and 5).

Secondary Analyses

Results from analyses in which follow-up was extended to include any MCMs ascertained from delivery until the end of the study period were almost identical (Table 2). In models examining MCM subgroups, there was evidence of an increased rate of limb malformations following first-trimester vaccination (HR, 1.20; 99% CI, 1.00–1.44; $P = .01$) (Table 3). Adjusting for a priori or all potential confounders removed this association (HR, 1.03; 99% CI, .86–1.25; $P = .66$). Results were similar for other trimesters. For congenital heart defects, no association was seen with vaccination in any model.

Sensitivity Analyses

Sensitivity analyses that included 216 additional pregnancies for which vaccination occurred 4 weeks prior to their estimated start, or allowed for follow-up in HES and ONS data to continue after follow-up in CPRD had ended, or excluded 8093 pregnancies of women with unknown BMI did not differ substantially from the main analyses (Table 4).

DISCUSSION

This UK-based historical cohort study examined the association between SIV during pregnancy and MCMs in live-born infants, between the 2010/2011 and 2015/2016 influenza seasons. Based on 6872 pregnancies vaccinated in the first trimester, there was no evidence for an association with MCMs recorded in the year after delivery (adjusted HR, 1.06; 99% CI, .94–1.19; $P = .2$). No evidence of an association was seen in analyses assessing subsequent trimesters or pregnancy overall or analyses including MCMs recorded after delivery and anytime in the study period. Analyses of major limb and congenital heart defects adjusted for confounding also showed no evidence for an association with first-trimester or later vaccination.

Strengths

Reviews examining the safety of influenza vaccination with respect to MCMs have highlighted the limited number of studies examining first-trimester vaccination with SIV. Among the few such studies, further limitations such as the low number of pregnant women vaccinated in the first trimester and short follow-up time of infants have prompted calls for further safety evidence [7, 8, 10, 11].

The utilization of the Pregnancy Register, which includes information on trimester dates, allowed for the identification of a large number of pregnant women vaccinated in the first trimester. Follow-up in most studies has been limited to the immediate period around delivery [13–15]. While a few studies have attempted follow-up for the year after delivery [12, 16], extending follow-up beyond 1 year has been shown to still

Table 3. Examining the Association Between Vaccination, Major Limb Malformations, and Congenital Heart Defects

Time of Vaccination During Pregnancy (No. of Pregnancies)	No. of MCMs/Person-years (Rate per 100 Person-years)	HR, Unadjusted (99% CI)	*P*	HR, Adjusted for A Priori Confounders (99% CI)	*P*	HR, Adjusted for All Potential Confounders (99% CI)	*P*
Models including limb malformations ascertained after delivery and anytime in the study period (N = 2425 limb malformations)							
Never (46 669)	1350/107 080 (1.3)	1.00		1.00		1.00	
Any trimester (31 481)	1075/56 940 (1.9)	1.20 (1.08–1.33)	<.001	1.10 (.99–1.23)	.03	1.07 (.96–1.21)	.11
Trimester 1 (6872)	235/12 259 (1.9)	1.20 (1.00–1.44)	.01	1.07 (.89–1.29)	.34	1.03 (.86–1.25)	.66
Trimester 2 (11 678)	405/21 145 (1.9)	1.22 (1.06–1.41)	<.001	1.11 (.96–1.29)	.07	1.09 (.93–1.27)	.17
Trimester 3 (12 931)	435/23 536 (1.9)	1.18 (1.02–1.36)	.003	1.11 (.96–1.28)	.07	1.09 (.94–1.26)	.14
Models including congenital heart defects ascertained after delivery and anytime in the study period (N = 789 heart defects)							
Never (46 669)	479/109 133 (0.4)	1.00		1.00		1.00	
Any trimester (31 481)	310/58 303 (0.5)	.99 (.82–1.20)	.90	.96 (.79–1.17)	.58	.93 (.76–1.15)	.39
Trimester 1 (6872)	67/12 568 (0.5)	.97 (.69–1.36)	.82	.93 (.66–1.31)	.58	.91 (.64–1.29)	.49
Trimester 2 (11 678)	129/21 621 (0.6)	1.12 (.87–1.44)	.26	1.08 (.83–1.41)	.45	1.04 (.79–1.37)	.68
Trimester 3 (12 931)	114/24 114 (0.5)	.89 (.68–1.16)	.25	.87 (.66–1.14)	.18	.85 (.65–1.13)	.14

A priori confounders were maternal age, maternal ethnicity, region, and influenza season. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension, and exposure to teratogenic drugs and/or live vaccines.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; IMD, Index of Multiple Deprivation; MCM, major congenital malformation.

Table 4. Examining the Association Between First-Trimester Vaccination and Major Congenital Malformations in Sensitivity Analyses

Models	HR, Unadjusted (99% CI)	*P*	HR, Adjusted for A Priori Confounders (99% CI)	*P*	HR, Adjusted for All Potential Confounders (99% CI)	*P*
Models including MCMs diagnosed in the year after delivery						
Main model	1.17 (1.04–1.32)	<.001	1.08 (.96–1.22)	.11	1.06 (.94–1.19)	.23
Including pregnancies vaccinated in the 4 weeks prior to the start[a]	1.19 (1.06–1.33)	<.001	1.09 (.97–1.23)	.06	1.07 (.95–1.21)	.14
Including diagnoses made beyond truncation of follow-up in CPRD[b]	1.17 (1.04–1.32)	<.001	1.08 (.96–1.22)	.11	1.06 (.94–1.19)	.23
Excluding pregnancies with unknown BMI[c]	1.18 (1.05–1.33)	<.001	1.09 (.96–1.23)	.09	1.07 (.94–1.21)	.19
Models including MCMs diagnosed after delivery and anytime in the study period						
Main model	1.18 (1.05–1.32)	<.001	1.09 (.97–1.22)	.07	1.07 (.95–1.20)	.16
Including pregnancies vaccinated in the 4 weeks prior to the start[a]	1.19 (1.07–1.33)	<.001	1.10 (.98–1.24)	.03	1.08 (.96–1.21)	.09
Including diagnoses made beyond truncation of follow-up in CPRD[d]	1.17 (1.05–1.31)	<.001	1.09 (.97–1.22)	.06	1.07 (.95–1.20)	.14
Excluding pregnancies with unknown BMI[c]	1.18 (1.05–1.33)	<.001	1.09 (.96–1.23)	.08	1.07 (.95–1.21)	.16

A priori confounders were maternal age, maternal ethnicity, region, and influenza season. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension, and exposure to teratogenic drugs and/or live vaccines.

Abbreviations: BMI, body mass index; CI, confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics database; HR, hazard ratio; IMD, Index of Multiple Deprivation; MCM, major congenital malformation; ONS, Office for National Statistics death certificate data.

[a]This model included an additional 216 pregnancies with a vaccination in the 4 weeks before the pregnancy start.

[b]There were 22 infants with an MCM recorded in HES or ONS after follow-up in the CPRD had ended.

[c]This model excluded 8093 pregnancies that belonged to women with unknown BMI.

[d]There were 110 infants with an MCM recorded in HES or ONS after follow-up in the CPRD had ended.

increase the prevalence of recorded MCMs in CPRD [18, 19, 29]. The majority of infants in our cohort had at least 1 year of follow-up and almost half had at least 2 years of follow-up. The value of longer follow-up is demonstrated by the fact that 12.8% of MCMs in our cohort were identified after 3 months and 5.3% after 1 year.

A further strength of this study was the linkage of CPRD data to HES and ONS to maximize MCM ascertainment. Previous research suggests that reliance on sole data sources can lead to significant underascertainment of conditions [30]. This may be particularly true for MCMs, many of which are likely to be identified in hospital and communicated in letters not available to researchers in the electronic primary care record unless encoded, which may be incomplete or delayed. Linkage to ONS further serves to ascertain those cases that may have been detected following the infant's death. For completeness, we also examined MCM recordings made in HES or ONS after follow-up in CPRD had ended, but this made minimal difference.

Limitations

While our study had a number of strengths, there were also limitations. Coding algorithms to identify MCMs were developed in accordance with EUROCAT guidelines and with a consultant neonatologist. The few studies that have assessed the positive-predictive value of MCMs recorded in CPRD have found this to be good overall (78–86%), with results for congenital heart defects being above 90% [31–34]. However, validation of diagnoses in HES has not been undertaken.

The estimate of gestation at the time of vaccination is based on the Pregnancy Register's use of a wide range of information recorded in primary care, which is thought to give rise to increased accuracy. However, any imprecision in the estimated pregnancy start date could result in misclassification of the timing of vaccination during pregnancy. Sensitivity analyses including pregnant women who received SIV in the 4 weeks prior to their pregnancy start went some way in addressing this and did not reveal evidence for an association with MCMs. In addition to the above, while general practitioners are required to document vaccinations received outside of the surgery and the maternal influenza vaccination program was delivered almost entirely through general practices over the study period, misclassification of vaccination could potentially occur if women were vaccinated elsewhere and practitioners were not notified [35].

We adjusted for a number of potential confounders but were not always able to determine maternal smoking, hazardous drinking, or BMI at the start of pregnancy and sometimes had to rely on the most proximate record. Although in our main analyses women with unknown BMI were categorized as not having any evidence of extreme BMI, our sensitivity analyses excluding these pregnancies yielded similar results. We cannot discount the possibility of residual confounding from other risk factors for MCMs that may also be associated with vaccine uptake in pregnancy and that are likely to be poorly recorded in the CPRD, such as religion [36].

This study only examined live-birth pregnancies with linked infant records, excluding 10.6% of pregnancies because they

lacked linkage. There are many reasons for nonlinkage, including the general practice ending data contributions to CPRD or the mothers moving away. It is possible that severe malformations resulting in the death or prolonged hospitalization of neonates could also prevent linkage, but it seems unlikely that this incomplete ascertainment would depend on maternal vaccination status. This study also did not explore any potential role of malformations on the causal pathway between vaccination and pregnancy losses. However, studies thus far have found no evidence for an association between vaccination and such outcomes [10, 37, 38].

Comparison With Other Studies

Our results are consistent with those from other studies that have examined SIV receipt during pregnancy and have shown no association with MCMs; this includes analyses of first-trimester vaccination for which point estimates from other studies ranged between 0.67 and 1.91, with CIs including the null [12, 13, 15, 16]. Reassuringly, our point estimates for MCMs following first-trimester vaccination are in line with those from the largest study to date, which examined SIV receipt between 2004 and 2013 in the United States (adjusted prevalence ratio, 1.02; 95% CI, .94–1.10; P = .55) [16]. Ours is the next largest study and provides further evidence on the safety of SIV during pregnancy in another setting and for subsequent years using a recently developed Pregnancy Register that considers all available data in the CPRD to estimate gestation at the time of vaccination as well as maximizing ascertainment of MCMs through long-term follow-up in linked data.

The lack of an association between first-trimester vaccination and congenital heart defects in our study was consistent with results from 2 other studies, including the large US study [13, 16]. While other studies have examined limb malformations and have not found any association with vaccination, they have grouped these with defects in other organ systems or examined a limited selection of particular diagnoses such as talipes equinovarus (clubfoot) [13, 16]. This study assessed all major limb malformations as a stand-alone subgroup and confirmed the lack of association with SIV.

CONCLUSIONS

The findings from this large cohort study, in which the majority of infants were followed up for at least 1 year, provide further evidence on the safety profile of influenza vaccination in pregnancy. There was no evidence for an association between first-trimester vaccination and MCMs, limb malformations, or congenital heart defects after controlling for confounding. This study shows ongoing monitoring of the safety of first-trimester vaccination is possible using CPRD and could usefully include additional MCM subgroups when sufficient numbers become available.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Study concept and design: all authors. Acquisition of data: S. L. T., C. M., M. P., P. M., J. L. W., and N. J. A. Analysis and interpretation of data: M. P., S. L. T., P. M., C. M., H. I. M., J. L. W., and N. J. A. Drafting of the manuscript: M. P., P. M., C. M., and H. I. M. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: M. P., S. L. T., C. M., J. L. W., and N. J. A. Obtained funding: S. L. T., and P. M. and M. P. had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analyses.

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