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Association Between Pandemic Influenza A(H1N1) Vaccination in Pregnancy and Early Childhood Morbidity in Offspring

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IMPORTANCE Several studies investigating potential adverse effects of the pandemic A(H1N1) vaccine have supported that influenza A(H1N1) vaccination does not increase the risk for major pregnancy and birth adverse outcomes, but little is known about possible adverse effects in offspring of A(H1N1)-vaccinated mothers beyond the perinatal period and into early childhood.

OBJECTIVE To evaluate whether pandemic influenza A(H1N1) vaccination in pregnancy increases the risk for early childhood morbidity in offspring.

DESIGN, SETTING, AND PARTICIPANTS Register-based cohort study comprising all live-born singleton children in Denmark from pregnancies overlapping the A(H1N1) influenza vaccination campaign in Denmark, from November 2, 2009, to March 31, 2010. From a cohort of 61 359 pregnancies, offspring exposed and unexposed to the influenza A(H1N1) vaccine during pregnancy were matched 1:4 on propensity scores.

EXPOSURE Vaccination in pregnancy with a monovalent inactivated AS03-adjuvanted split virion influenza A(H1N1)pdm09 vaccine (Pandemrix; GlaxoSmithKline Biologicals).

MAIN OUTCOMES AND MEASURES Rate ratios of hospitalization in early childhood until 5 years of age. Hospitalization was defined as (1) first inpatient hospital admission, (2) all inpatient hospital admissions, and (3) first hospital contact for selected diseases, which included individual infectious diseases and individual neurologic, autoimmune, and behavioral conditions.

RESULTS The mean (SD) age at end of follow-up was 4.6 (0.40) years for the 61 359 children included in the study. In the cohort, the mothers of 55 048 children were unvaccinated, 349 mothers were vaccinated in the first trimester, and 5962 mothers were vaccinated in the second or third trimesters. Children exposed in the first trimester were not more likely to be hospitalized in early childhood than unexposed children (hospitalization rates per 1000 person-years, 300.6 for exposed vs 257.5 for unexposed; rate ratio, 1.17; 95% CI, 0.94-1.45). Similarly, children exposed in the second or third trimester were not more likely to be hospitalized in early childhood than unexposed children (hospitalization rates per 1000 person-years, 203.6 for exposed vs 219.3 for unexposed; rate ratio, 0.93; 95% CI, 0.87-0.99). This 7% decreased risk was primarily a result of reduced risks for infectious disease–related hospitalizations.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the most comprehensive study to date of potential adverse effects manifesting after the perinatal period. We detected no increased risk for early childhood morbidity. These results support the safety profile of the influenza A(H1N1) vaccine used in pregnancy.

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Supplemental content

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Pregnant women are prone to a number of physiological changes that put them at increased risk for severe disease and death from influenza.[1] The presence of comorbid conditions, such as asthma, diabetes, and obesity, can exacerbate this risk.[2]

In particular, during 20th-century pandemics, disproportionate rates of severe influenza infection among pregnant women have been observed in numerous studies.[3-5] More recently, during the 2009 pandemic, case reports of increased morbidity and mortality in otherwise healthy pregnant women indicated that pregnant women infected with influenza A(H1N1) were at substantially higher risk for hospitalization and intensive care unit admissions with a disproportionately severe clinical course.[2,6-9] During the 2009-2010 vaccination season, influenza vaccination with inactivated monovalent vaccines was recommended to all pregnant women and increased vaccination rates were observed in a number of countries.[10,11]

Influenza vaccines can provide moderate protection against influenza infection in healthy adults, depending on how well the vaccine composition matches the circulating strains.[12,13] In pregnant women, an additional protective effect can be achieved for their infants.[14,15]

As with any health care intervention, especially when preventive and given to the vulnerable population of pregnant women, maternal influenza vaccination needs a solid evidence base regarding its safety. Several studies investigating potential adverse effects of the pandemic A(H1N1) vaccine have supported that influenza A(H1N1) vaccination does not increase the risk for major pregnancy and birth adverse outcomes, such as birth defects, fetal death, intrauterine growth restriction, and preterm delivery.[16-18]

However, there is a dearth of studies looking at adverse effects in the offspring of A(H1N1)-vaccinated mothers beyond the perinatal period and into early childhood. To provide further insights into potential adverse effects manifesting outside of the perinatal period, we conducted a study of long-term adverse events following pandemic influenza A(H1N1) vaccination in pregnancy in the general Danish population including 6308 vaccinated pregnant women.

Key Points

Question Is pandemic influenza A(H1N1) vaccination in pregnancy associated with an increased risk for early childhood morbidity in offspring?

Findings In this cohort study, children exposed to maternal vaccination during pregnancy were not significantly more likely to be hospitalized in early childhood than unexposed children.

Meaning These results support the safety profile of influenza A(H1N1) vaccine used in pregnancy.

Methods

Cohort

The study included live-born children from pregnancies that overlapped the A(H1N1) influenza vaccination campaign in Denmark, which was defined as November 2, 2009, to March 31, 2010. We defined the study cohort using the Danish Medical Birth Registry.[19] This register holds information on all deliveries by women living in Denmark. The recorded information on each birth includes date of delivery, gestational age, and a range of other information about the newborn and the course of pregnancy and delivery. Also included is a range of information about the mother (eg, parity, body mass index, and smoking status). Gestational age in the Medical Birth Registry is defined on the basis of the first day of the last menstrual period and is for most women corrected by ultrasonography in the late first or early second trimester. The onset of pregnancy was defined as the first day of the last menstrual period and was calculated by subtracting the recorded gestational age from the date of birth. Information on death, emigration, and disappearance from national registers (eg, emigrating without informing authorities) of the children in the cohort was obtained from the Danish Civil Registration System.[20]

This study was approved by the Danish Data Protection Agency; informed consent is not required for register-based research in Denmark.

We restricted the cohort to include singleton children born to women who were 18 to 44 years of age at pregnancy onset. Among mothers who had more than 1 pregnancy overlapping the study period, only the first was included. We also excluded births with a gestational age of less than 32 weeks (because preterm birth shortens the period of vaccination during pregnancy); births among women who had lived less than 5 years in Denmark (to ensure adequate capture of covariate information for the mothers); births among women who had been vaccinated before pregnancy onset; and children with diagnoses of chromosomal aberrations, genetic disorders, birth defect syndromes with known causes, and congenital viral infections possibly associated with birth defects (rubella, cytomegalovirus, herpes simplex, hepatitis, other viral infections including varicella, and unspecified congenital viral disease).

Vaccinations

Information on vaccination status and date of vaccination for the mothers was obtained from the national A(H1N1) vaccination database, established at Statens Serum Institute.[21] In Denmark, the only vaccine used was the monovalent inactivated AS03-adjuvanted split virion influenza A(H1N1)pdm09 vaccine (Pandemrix; GlaxoSmithKline Biologicals). During the campaign, clinics administering the A(H1N1) vaccine were mandated by law to report all vaccinations to the Danish Board of Health. Furthermore, reimbursement from the Danish Health Insurance was made only after information on dates and details had been reported. Information on vaccinations may therefore be considered close to complete.

The A(H1N1) vaccination campaign in Denmark targeted individuals with chronic diseases, key government officials, public-safety workers, and pregnant women.[22] Pregnant women with chronic disease were recommended to get vaccinated during their first trimester. Pregnant women without chronic disease could get vaccinated after individual assessment by a physician.

Propensity Score Models

We estimated 2 separate propensity score models[23] for maternal A(H1N1) vaccination in the first and second to third trimester. The first model included children whose mothers were vaccinated in the first trimester and children whose mothers were not vaccinated during pregnancy. Correspondingly, the second model included children whose mothers were vaccinated in the second or third trimester and children whose mothers were not vaccinated. Both models included the same predictors. All variables included in the propensity score models are listed in **Table 1**. After propensity score estimation, we created 2 distinct propensity score–matched cohorts for maternal vaccination in the first and second to third trimester. The propensity score matching was conducted using the nearest neighbor–matching algorithm (caliper width of 0.05 of the SD of the logit score) on a ratio of 1:4. Standardized mean differences were calculated to assess balance. Covariates with differences less than 10% were considered well balanced.

Outcomes

All outcomes were based on information from the Danish National Patient Register.[24] This nationwide register holds information on all hospital contacts in Denmark, including date of admission and discharge, setting of care (in terms of outpatient, inpatient, and emergency department services), and diagnoses (classified according to *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes).

For the analyses of first hospitalization and all hospitalizations (the primary study outcomes), the outcomes were based on any inpatient hospital admission after start of follow-up. In the analysis of all hospitalizations, the number of hospitalizations was based on a definition in which a new admission was required to be preceded by at least 1 day outside hospital since the date of previous hospital discharge. For the analyses of individual infectious diseases and individual neurologic, autoimmune, and behavioral conditions, the outcomes were based on primary and secondary diagnoses codes identified from inpatient and outpatient hospital contacts. Specific *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes for the included individual conditions are presented in the eTable 1 in the Supplement.

The children in the cohort were followed up from the date of hospital discharge after birth. For the analyses of first hospitalization, follow-up was censored at the date of the first hospital admission. For the analyses of individual conditions, follow-up was censored at the date of an event of the individual outcome under study. Other censoring criteria for all analyses were death, emigration, or disappearance; becoming 5 years of age; and end of follow-up (December 31, 2014).

Statistical Analysis

The analysis of first hospitalization was conducted using proportional hazards regression yielding hazard ratios (HRs). The analyses of individual conditions and all hospitalizations were conducted using Poisson regression yielding rate ratios (RRs).[25] For the latter analysis, generalized estimating equations[26] were used to take into account the possibility of nonindependence between consecutive hospital admissions in the same child.

For covariates with missing values, we treated missing values as a separate category except for variables with very few missing values (<1.0%) where we used mode imputation. The proportion of missing was less than 5% for all 5 covariates that had missing values (Table 1). We considered effect estimates to be statistically significant if the 95% CI did not overlap 1. Analyses were performed with SAS software version 9.4 (SAS Institute).

Results

We identified a total of 69 598 children from pregnancies that overlapped the A(H1N1) vaccination period; 61 359 children were available for study inclusion: 55 048 with unvaccinated mothers, 349 with mothers who were vaccinated in the first trimester, and 5962 with mothers who were vaccinated in the second or third trimester (**Figure 1**).

First Trimester Cohort

The baseline characteristics of mothers vaccinated in the first trimester before propensity score matching are shown in Table 1. Compared with mothers who were unvaccinated, mothers vaccinated in the first trimester were more likely to be in the age group of 35 to 44 years of age; were more likely to be overweight or obese and less likely to be of normal weight; were more likely to have had a diagnosis of cardiovascular, neurological, and rheumatic disease, as well as inflammatory bowel disease and disorders of the genital tract; were more likely to have been hospitalized for more than 5 days in the year prior to pregnancy; had more outpatient hospital contacts; and had more prescription drug use, both in terms of treatments for specific conditions and the number of different drugs used.

The matched cohort included 347 children to vaccinated mothers and 1383 children to unvaccinated mothers. After propensity score matching, unvaccinated and vaccinated mothers were similar on all measured characteristics; the baseline characteristics of the matched cohort are shown in Table 1. Standardized mean differences are shown in eTable 2 in the Supplement; all covariates were well balanced.

The results from the analyses of first hospitalization are shown in **Figure 2**A. A total of 858 children were hospitalized during follow-up: 675 children to unvaccinated mothers (rate of hospitalization per 1000 person-years, 171.6) and 183 children to mothers vaccinated in the first trimester (rate of hospitalization, 199.3). The risk for first hospitalization was not significantly higher among children to mothers vaccinated in the first trimester compared with children of unvaccinated mothers at 5 years' follow-up (HR, 1.13; 95% CI, 0.96-1.32). The estimates were similar at 1 and 3 years' follow-up.

Table 2 shows the results from the analysis of all hospitalizations. Maternal first trimester vaccination was not associated with an increased number of hospitalizations at 5 years' follow-up (RR, 1.17; 95% CI, 0.94-1.45). Similarly, the number of hospitalizations was not significantly higher at 1 or 3 years' follow-up.

Table 1. Maternal Characteristics According to Pandemic Influenza A Vaccination in Pregnancy

Characteristic	Vaccination, No. (%)				
	Matched Cohort (n = 1730)		Matched Cohort (n = 29 563)		Unmatched Cohort (n = 61 359)
	None (n = 1383)	First Trimester (n = 347)	None (n = 23 603)	Second or Third Trimester (n = 5961)	None (n = 55 048)
Maternal age at pregnancy onset, mean (SD)	30.5 (5.2)	30.7 (5.1)	30.8 (4.8)	30.9 (4.7)	30.1 (4.9)
Maternal age at pregnancy onset, y					
18-24	212 (15.3)	50 (14.4)	2682 (11.4)	647 (10.9)	8550 (15.5)
25-34	885 (64.0)	225 (64.8)	16 205 (68.7)	4148 (69.6)	37 333 (67.8)
35-44	286 (20.7)	72 (20.7)	4716 (20.0)	1166 (19.6)	9165 (16.6)
Maternal place of birth[a]					
Denmark	1203 (87.0)	309 (89.0)	21 197 (89.8)	5383 (90.3)	49 161 (89.3)
Europe	39 (2.8)	10 (2.9)	696 (2.9)	169 (2.8)	1204 (2.2)
Outside Europe	141 (10.2)	28 (8.1)	1710 (7.2)	409 (6.9)	4683 (8.5)
Region of residence[b]					
Copenhagen	455 (32.9)	121 (34.9)	8641 (36.6)	2208 (37.0)	18 383 (33.4)
Central Jutland	328 (23.7)	77 (22.2)	5445 (23.1)	1385 (23.2)	12 927 (23.5)
North Jutland	139 (10.1)	35 (10.1)	2158 (9.1)	529 (8.9)	5443 (9.9)
Sealand	135 (9.8)	35 (10.1)	2399 (10.2)	578 (9.7)	6956 (12.6)
South Denmark	326 (23.6)	79 (22.8)	4960 (21.0)	1261 (21.2)	11 339 (20.6)
Marital status					
Married/living with partner	1027 (74.3)	259 (74.6)	18 896 (80.1)	4799 (80.5)	41 789 (75.9)
Single	356 (25.7)	88 (25.4)	4707 (19.9)	1162 (19.5)	13 259 (24.1)
Education[c]					
Primary/secondary school	542 (39.2)	127 (36.6)	7025 (29.8)	1702 (28.6)	18 686 (33.9)
Short tertiary education	423 (30.6)	105 (30.3)	6896 (29.2)	1735 (29.1)	16 926 (30.7)
Medium or long tertiary education	418 (30.2)	115 (33.1)	9682 (41.0)	2524 (42.3)	19 436 (35.3)
Household income, yearly tertiles					
First	514 (37.2)	128 (36.9)	6879 (29.1)	1700 (28.5)	18 623 (33.8)
Second	428 (30.9)	107 (30.8)	7855 (33.3)	1984 (33.3)	18 360 (33.4)
Third	441 (31.9)	112 (32.3)	8869 (37.6)	2277 (38.2)	18 065 (32.8)
Maternal BMI at pregnancy onset[d]					
<18.5	54 (3.9)	13 (3.7)	975 (4.1)	225 (3.8)	2095 (3.8)
18.5-24.9	647 (46.8)	167 (48.1)	13 268 (56.2)	3481 (58.4)	32 338 (58.7)
25.0-29.9	337 (24.4)	86 (24.8)	5016 (21.3)	1216 (20.4)	11 438 (20.8)
30.0-34.9	151 (10.9)	32 (9.2)	2058 (8.7)	473 (7.9)	4526 (8.2)
≥35	111 (8.0)	32 (9.2)	1394 (5.9)	347 (5.8)	2346 (4.3)
Missing	83 (6.0)	17 (4.9)	892 (3.8)	219 (3.7)	2305 (4.2)
Maternal smoking at pregnancy onset[e]					
Yes	216 (15.6)	50 (14.4)	2984 (12.6)	700 (11.7)	7212 (13.1)
Missing	38 (2.7)	10 (2.9)	379 (1.6)	92 (1.5)	1119 (2.0)
Maternal parity					
0	551 (39.8)	139 (40.1)	8967 (38.0)	2242 (37.6)	24 198 (44.0)
1-2	739 (53.4)	190 (54.8)	13 572 (57.5)	3470 (58.2)	28 480 (51.7)
≥3	93 (6.7)	18 (5.2)	1064 (4.5)	249 (4.2)	2370 (4.3)
Medical history					
Respiratory disease	75 (5.4)	18 (5.2)	597 (2.5)	156 (2.6)	894 (1.6)
Cardiovascular disease	68 (4.9)	16 (4.6)	602 (2.6)	152 (2.5)	1071 (1.9)
Hematological disease	27 (2.0)	8 (2.3)	436 (1.8)	108 (1.8)	734 (1.3)
Neurological disease	87 (6.3)	25 (7.2)	1176 (5.0)	292 (4.9)	2006 (3.6)
Liver and kidney disease	21 (1.5)	4 (1.2)	243 (1.0)	60 (1.0)	542 (1.0)
Rheumatic disease	49 (3.5)	11 (3.2)	293 (1.2)	75 (1.3)	481 (0.9)
Inflammatory bowel disease	55 (4.0)	14 (4.0)	339 (1.4)	85 (1.4)	600 (1.1)
Disorders of female pelvic organs/genital tract	319 (23.1)	78 (22.5)	4571 (19.4)	1079 (18.1)	9228 (16.8)

(continued)

Table 1. Maternal Characteristics According to Pandemic Influenza A Vaccination in Pregnancy (continued)

Characteristic	Vaccination, No. (%)				
	Matched Cohort (n = 1730)		Matched Cohort (n = 29 563)		Unmatched Cohort (n = 61 359)
	None (n = 1383)	First Trimester (n = 347)	None (n = 23 603)	Second or Third Trimester (n = 5961)	None (n = 55 048)
Duration of hospitalization in the previous year, d					
0	1031 (74.5)	265 (76.4)	18 367 (77.8)	4721 (79.2)	44 409 (80.7)
1-4	261 (18.9)	58 (16.7)	3909 (16.6)	921 (15.5)	8250 (15.0)
≥5	91 (6.6)	24 (6.9)	1327 (5.6)	319 (5.4)	2389 (4.3)
No. of outpatient contacts in the previous year					
0	715 (51.7)	187 (53.9)	14 714 (62.3)	3831 (64.3)	36 582 (66.5)
1	426 (30.8)	98 (28.2)	5713 (24.2)	1367 (22.9)	11 952 (21.7)
≥2	242 (17.5)	62 (17.9)	3176 (13.5)	763 (12.8)	6514 (11.8)
Prescription drug use					
β-2 Agonist inhalants	152 (11.0)	36 (10.4)	1152 (4.9)	290 (4.9)	1863 (3.4)
Corticosteroid inhalants	82 (5.9)	21 (6.1)	462 (2.0)	127 (2.1)	594 (1.1)
Cardiovascular drugs	57 (4.1)	17 (4.9)	883 (3.7)	232 (3.9)	1371 (2.5)
Oral antidiabetic drugs	38 (2.7)	12 (3.5)	498 (2.1)	117 (2.0)	826 (1.5)
Insulin	34 (2.5)	12 (3.5)	138 (0.6)	53 (0.9)	158 (0.3)
Intestinal anti-inflammatory agents	29 (2.1)	8 (2.3)	179 (0.8)	49 (0.8)	262 (0.5)
Immunosuppressants	21 (1.5)	7 (2.0)	95 (0.4)	33 (0.6)	109 (0.2)
Antidepressants	139 (10.1)	33 (9.5)	1845 (7.8)	431 (7.2)	3589 (6.5)
Anxiolytics, hypnotics, and sedatives	66 (4.8)	16 (4.6)	762 (3.2)	184 (3.1)	1271 (2.3)
Antiepileptics	25 (1.8)	6 (1.7)	192 (0.8)	49 (0.8)	456 (0.8)
Drugs for peptic ulcer/gastroesophageal reflux	102 (7.4)	23 (6.6)	1372 (5.8)	331 (5.6)	2512 (4.6)
Drugs for in vitro fertilization	155 (11.2)	36 (10.4)	2167 (9.2)	504 (8.5)	4353 (7.9)
Thyroid hormones	32 (2.3)	7 (2.0)	353 (1.5)	86 (1.4)	617 (1.1)
Systemic corticosteroids	50 (3.6)	13 (3.7)	700 (3.0)	180 (3.0)	1173 (2.1)
NSAIDs	238 (17.2)	60 (17.3)	4147 (17.6)	997 (16.7)	8335 (15.1)
Opiates	100 (7.2)	25 (7.2)	957 (4.1)	237 (4.0)	1889 (3.4)
No. of prescriptions for systemic antibacterial agents					
0	732 (52.9)	187 (53.9)	13 471 (57.1)	3463 (58.1)	33 898 (61.6)
1-3	567 (41.0)	138 (39.8)	9141 (38.7)	2250 (37.7)	19 421 (35.3)
≥4	84 (6.1)	22 (6.3)	991 (4.2)	248 (4.2)	1729 (3.1)
No. of drugs used					
0	111 (8.0)	27 (7.8)	2706 (11.5)	698 (11.7)	8020 (14.6)
1-4	712 (51.5)	185 (53.3)	14 875 (63.0)	3793 (63.6)	35 726 (64.9)
≥5	560 (40.5)	135 (38.9)	6022 (25.5)	1470 (24.7)	11 302 (20.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Total of 69 (0.1%) missing in the unmatched cohort.

[b] Total of 2 (<0.1%) missing in the unmatched cohort.

[c] Total of 319 (0.5%) missing in the unmatched cohort.

[d] Total of 2542 (4.1%) missing in the unmatched cohort.

[e] Total of 1221 (2.0%) missing in the unmatched cohort.

The analyses of individual infectious diseases and neurological and behavioral conditions are presented in **Figure 3**. First trimester maternal vaccination was not associated with a significantly increased risk for 22 of the 23 individual outcomes; the risk for other infections was increased (RR, 1.71; 95% CI, 1.08-2.73). Taking multiple comparisons into account using Bonferroni-corrected confidence intervals, there was no significantly increased risk (RR, 1.71; 95% CI, 0.83-3.56).

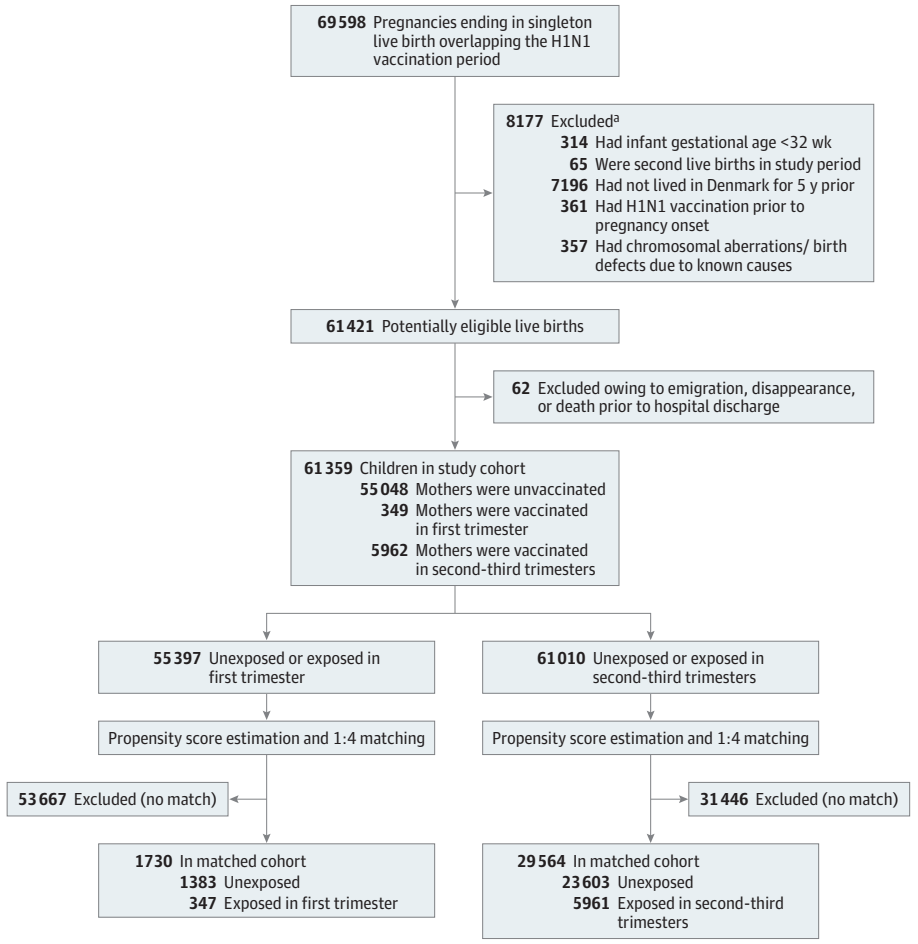
Second or Third Trimester Cohort

Characteristics of mothers vaccinated in the second or third trimester before matching are shown in Table 1. Vaccinated mothers were less likely to be 18 to 24 years of age; more likely to be married; more likely to have a medium or long tertiary education; more likely to have an income in the top distribution tertile; less likely to be nulliparous; and more likely to have 1 to 2 children.

After matching, the cohort for the analyses of second or third trimester vaccination included 5961 children to vaccinated mothers and 23 603 children to unvaccinated mothers; the 2 groups were well balanced on all measured prepregnancy maternal characteristics (Table 1 and eTable 2 in the Supplement).

Figure 2B shows the risk for first hospitalization in the matched cohort. During follow-up, 13 260 children were hospitalized: 10 633 children to unvaccinated (rate of

Figure 1. Flowchart of Study Design and Cohort Construction



Pregnancies eligible for study inclusion, exclusion criteria, and construction of the 2 study cohorts: 1 for pregnancies exposed to vaccination in the first trimester and 1 for pregnancies exposed to vaccination in the second or third trimester.

[a] Because it is possible to have more than 1 of the exclusion criteria, the numbers do not add up to 8177.

hospitalization, 151.6) and 2627 children to vaccinated mothers (rate of hospitalization, 137.5). Vaccination in the second or third trimester was not associated with an increased risk for first hospitalization at 5 years' follow-up (HR, 0.95; 95% CI, 0.91-0.99); risks were similar for second trimester vaccination (HR, 0.93; 95% CI, 0.87-0.99) and third trimester vaccination (HR, 0.98; 95% CI, 0.92-1.04). Truncating follow-up at 1 year (HR, 0.94; 95% CI, 0.89-0.99) and 3 years (HR, 0.95; 95% CI, 0.90-0.99) yielded similar results: no significantly increased risks.

Results from the analyses of all hospitalizations are shown in Table 2. Vaccination in the second or third trimester was not associated with an increased number of hospitalizations at 5 years' follow-up (RR, 0.93; 95% CI, 0.87-0.99); risks were similar for second trimester vaccination (RR, 0.92; 95% CI, 0.85-0.99) and third trimester vaccination (RR, 0.94; 95% CI, 0.85-1.03). Truncating follow-up at 1 year (RR, 0.93; 95% CI, 0.87-0.99) and 3 years (RR, 0.96; 95% CI, 0.90-1.01) yielded similar results: no significantly increased risks.

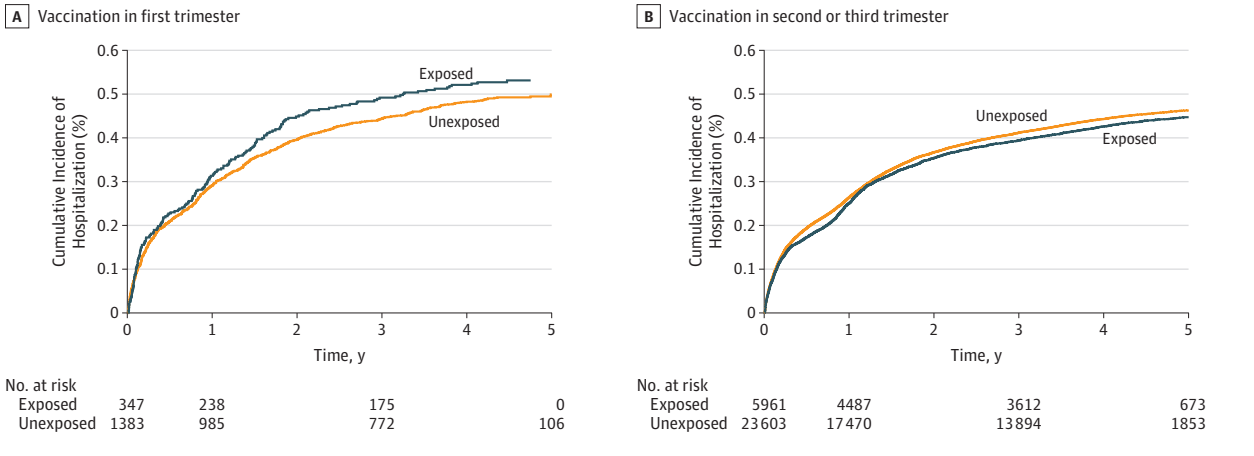
Figure 3 shows the results from the analyses of individual conditions. Vaccination in the second or third trimester was associated with a significantly increased risk for sepsis (RR, 1.96; 95% CI, 1.26-3.05) and Sjögren syndrome (RR, 1.59; 95% CI, 1.04-2.44). This was offset by significantly decreased risks for upper respiratory infections (RR, 0.92; 95% CI, 0.85-0.99) and gastrointestinal infections (RR, 0.84; 95% CI, 0.74-0.94). Taking multiple comparisons into account using Bonferroni-corrected confidence intervals, there was no significantly increased risk for sepsis (RR, 1.96; 95% CI, 0.98-3.91) and Sjögren syndrome (RR, 1.59; 95% CI, 0.82-3.11) or reduced risk for upper respiratory infections (RR, 0.92; 95% CI, 0.81-1.03) and gastrointestinal infections (RR, 0.84; 95% CI, 0.70-1.00).

Discussion

In this comprehensive cohort study of Danish children born to A(H1N1)-vaccinated mothers, we found no support for an increased risk for early childhood morbidity following A(H1N1) vaccination exposure.

Children exposed in the first trimester were more likely to be hospitalized but not statistically significantly so. However, we recognize that first trimester vaccination was rare in our cohort and that lack of statistical power cannot be discounted as an explanation for this null finding. Residual

Figure 2. Risk of First Hospitalization in Childhood According to Vaccination in Pregnancy



	Analysis Until First Year of Life	Analysis Until 3 y of Age	Analysis Until 5 y of Age (Main)
Exposed			
Events	108	170	183
Rate/1000 person-years	397.1	254.9	199.3
Unexposed			
Events	396	608	675
Rate/1000 person-years	358.0	216.3	171.6
Hazard Ratio (95% CI)	1.10 (0.89-1.37)	1.15 (0.97-1.37)	1.13 (0.96-1.32)

	Analysis Until First Year of Life	Analysis Until 3 y of Age	Analysis Until 5 y of Age (Main)
Exposed			
Events	1466	2.326	2.627
Rate/1000 person-years	295.8	182.0	137.5
Unexposed			
Events	6116	9.614	10.633
Rate/1000 person-years	317.2	193.5	151.6
Hazard Ratio (95% CI)	0.94 (0.89-0.99)	0.95 (0.90-0.99)	0.95 (0.91-0.99)

Cumulative incidences and hazard ratios of hospitalization comparing unexposed children and children exposed to vaccination in the first trimester (A) and second or third trimester (B).

Table 2. Rate Ratios of All Hospitalizations in Early Childhood Comparing Children From Influenza A Vaccinated and Unvaccinated Pregnancies

	Vaccination in First Trimester			Vaccination in Second or Third Trimester		
	Rate of Hospitalization per 1000 Person-Years			Rate of Hospitalization per 1000 Person-Years		
Age	Unvaccinated	Vaccinated	Rate Ratio (95% CI)	Unvaccinated	Vaccinated	Rate Ratio (95% CI)
1 y	490.3	566.1	1.15 (0.90-1.48)	417.8	387.8	0.93 (0.87-0.99)
3 y	316.3	384.2	1.21 (0.98-1.50)	276.7	264.6	0.96 (0.90-1.01)
5 y	257.5	300.6	1.17 (0.94-1.45)	219.3	203.6	0.93 (0.87-0.99)

confounding is also a possible explanation for the small increase in risk we observed. Although we used propensity score matching with a wide range of baseline maternal characteristics, it is possible that confounding by indication is still present.

Children exposed in the second or third trimester were not at an increased risk for hospitalization. These analyses were well powered statistically and we can exclude even small excess risks with a high degree of certainty. Instead, we observed statistically significant reductions in hospitalization risks of 7% for all hospitalizations until 5 years of age and 5% for the first hospitalization until 5 years of age.

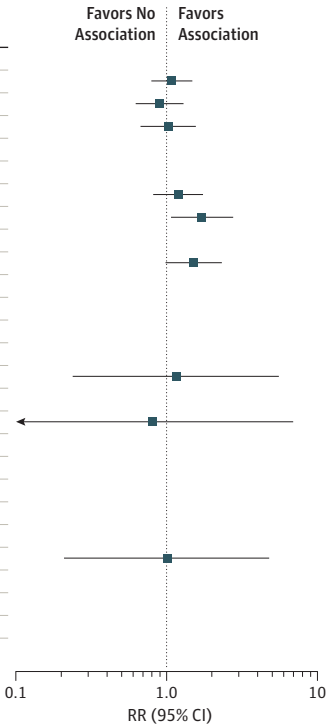
In the analyses of specific diseases in childhood, we observed significantly increased risks for other infections, sepsis, and Sjögren syndrome. We have no obvious explanation for these effects. The risks for sepsis and other infections are unlikely to reflect increased susceptibility to infections in general or bacterial infections in particular because we saw no increased risk for meningitis and significantly reduced risks for upper respiratory infections and gastrointestinal infections. However, multiple testing cannot be discounted as an explanation; we analyzed 2 exposure windows and 23 outcomes. Indeed, taking multiple comparisons into account using the Bonferroni correction, no significantly increased risks for other infections, sepsis, and Sjögren syndrome were observed.

Given that infectious diseases comprise most hospitalizations in early childhood, this group of outcomes is responsible for the reduced risks observed in all hospitalization outcomes. Although a reduced risk for both laboratory-confirmed influenza and influenzalike illness have been observed among infants of vaccinated mothers,[27] this effect is attributable to maternally transferred antibodies and is restricted to early infancy in contrast to the effects observed in our study, which persisted throughout early childhood and comprised infectious diseases other than influenzalike

Figure 3. Risk of Specific Diseases in Childhood According to Vaccination in Pregnancy

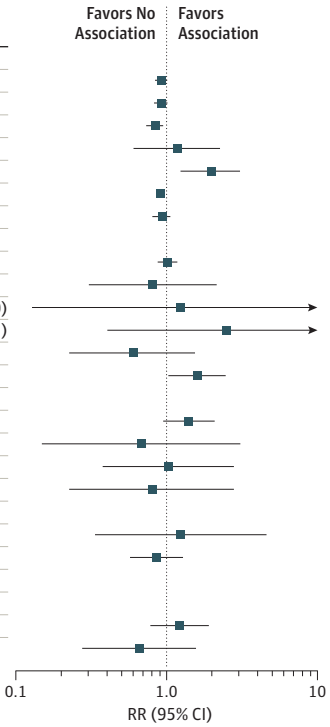
A Vaccination in first trimester

Specific Diseases in Childhood	Exposed No. of Events	Exposed IR/1000 PY	Unexposed No. of Events	Unexposed IR/1000 PY	RR (95% CI)
Infectious diseases					
Upper respiratory infection	54	38.4	202	35.4	1.08 (0.80-1.46)
Lower respiratory infection	38	26.5	168	29.6	0.90 (0.63-1.28)
Gastrointestinal infection	28	19.1	110	18.6	1.03 (0.68-1.55)
Meningitis	0	0	2	0.3	NE
Sepsis	0	0	5	0.8	NE
Viral infection	36	25.0	123	20.9	1.20 (0.82-1.73)
Other infection	25	16.9	60	9.8	1.71 (1.08-2.73)
Autoimmune diseases					
Asthma	30	20.6	82	13.7	1.50 (0.99-2.29)
Celiac disease	1	0.6	0	0	NE
Crohn disease	0	0	2	0.3	NE
Ulcerative colitis	0	0	0	0	NE
Juvenile arthritis	0	0	0	0.3	NE
Sjögren syndrome	2	1.3	7	1.1	1.15 (0.24-5.53)
Vasculitis	0	0	0	0	NE
Reactive arthropathy	1	0.6	5	0.8	0.80 (0.09-6.88)
Idiopathic thrombocytopenic purpura	0	0	2	0.3	NE
Idiopathic urticaria	0	0	0	0	NE
Type 1 diabetes	1	0.6	0	0	NE
Neurological diseases					
Bell palsy	0	0	0	0	NE
Epilepsy	2	1.3	8	1.3	1.01 (0.21-4.74)
Guillain-Barré syndrome	0	0	0	0	NE
Behavioral disorders					
Autistic disorder	0	0	3	0.5	NE
Mental retardation	0	0	2	0.3	NE



B Vaccination in second or third trimester

Specific Diseases in Childhood	Exposed No. of Events	Exposed IR/1000 PY	Unexposed No. of Events	Unexposed IR/1000 PY	RR (95% CI)
Infectious diseases					
Upper respiratory infection	776	29.2	3145	31.9	0.92 (0.85-0.99)
Lower respiratory infection	629	23.9	2550	26.1	0.92 (0.84-1.00)
Gastrointestinal infection	345	12.5	1529	15.0	0.84 (0.74-0.94)
Meningitis	12	0.4	38	0.4	1.17 (0.61-2.24)
Sepsis	30	1.1	57	0.5	1.96 (1.26-3.05)
Viral infection	472	17.4	1924	19.1	0.91 (0.82-1.00)
Other infection	295	10.6	1189	11.5	0.92 (0.81-1.05)
Autoimmune diseases					
Asthma	298	10.8	1091	10.6	1.02 (0.89-1.16)
Celiac disease	5	0.2	23	0.2	0.81 (0.31-2.12)
Crohn disease	1	0	3	<0.1	1.24 (0.31-11.90)
Ulcerative colitis	2	0.1	3	0.0	2.48 (0.41-14.82)
Juvenile arthritis	5	0.2	31	0.3	0.60 (0.23-1.54)
Sjögren syndrome	30	1.0	70	0.7	1.59 (1.04-2.44)
Vasculitis	0	0	2	<0.1	NE
Reactive arthropathy	37	1.3	98	0.9	1.40 (0.96-2.05)
Idiopathic thrombocytopenic purpura	2	0.1	11	0.1	0.68 (0.15-3.05)
Idiopathic urticaria	5	0.2	18	0.2	1.03 (0.38-2.78)
Type 1 diabetes	3	0.1	14	0.1	0.80 (0.23-2.77)
Neurological diseases					
Bell palsy	3	0.1	9	0.1	1.24 (0.34-4.57)
Epilepsy	30	1.1	130	1.2	0.86 (0.58-1.27)
Guillain-Barré syndrome	0	0	2	<0.1	NE
Behavioral disorders					
Autistic disorder	27	0.9	82	0.8	1.22 (0.79-1.86)
Mental retardation	6	0.2	34	0.3	0.66 (0.28-1.56)



Rate ratios (RRs) with 95% CIs comparing disease risk in unexposed children and children exposed to vaccination in the first trimester (A) and second or third trimester (B). IR indicates incidence ratio; NE, not estimable; PY indicates person-years.

illness. Further studies looking at individual infectious diseases in greater detail would be necessary to confirm and elucidate the reduced risks observed in our cohort.

To our knowledge, few studies have been published on possible adverse effects extending into early childhood after A(H1N1) vaccination exposure during fetal life. Ludvigsson and colleagues[28] conducted a Swedish cohort study of maternal A(H1N1) vaccination and offspring mortality. No increased risk of stillbirth, early neonatal death (days 0-6 after birth), or early childhood death (7 days-4.6 years) was observed. Van der Maas and colleagues[29] conducted a cross-sectional linkage study in the Netherlands with extensive questionnaire data on adverse pregnancy outcomes, growth and development of the offspring, and general practitioner contacts for infectious diseases during the first year of life. All outcomes evaluated, including infection-related contact rates, were similar in A(H1N1)-vaccinated and -unvaccinated pregnancies.

Strengths and Limitations

The main strength of our study was its comprehensive design with register linkage of individual-level data. Information on A(H1N1) vaccination and study outcomes was obtained through an independent nationwide database, with mandatory reporting improving the accuracy of information and reducing bias. We used a propensity score–matched design incorporating a large number of maternal characteristics to control for potential confounding. Our study also had a number of limitations. Vaccination was rare in the first trimester in our cohort, limiting the conclusions that can be drawn from our results. Although, we did include a wide range of maternal characteristics, we cannot exclude residual confounding, especially in the first trimester cohort, where vaccination was offered to mothers with chronic diseases and high-risk pregnancies. Our study attempted to describe early childhood morbidity in vaccinated and unvaccinated pregnancies. Our results are primarily applicable in the context of hospitalizations in general and the specific diseases we chose to include and to the monovalent inactivated AS03-adjuvanted split virion influenza A(H1N1)pdm09 vaccine used in Denmark. Given the continually changing composition of seasonal influenza vaccines, it will always be difficult to provide comprehensive postlicensure safety studies in a timely manner. However, with respect to current and future seasonal influenza vaccines, we believe it is reasonable to assume that our results contribute to the safety profiles of both AS03-adjuvanted and influenza A(H1N1)-containing vaccines used during pregnancy.

Conclusions

To our knowledge, this is the most comprehensive study to date of potential adverse effects manifesting after the perinatal period. We hope that other researchers can use the study as a template to explore early childhood effects of vaccination in pregnancy, an area of vaccine safety research that is almost completely unexplored.

In conclusion, our results support the overall safety profile of the influenza A(H1N1)pdm09 vaccine for use during pregnancy and support World Health Organization recommendations that pregnant women should be vaccinated with influenza vaccine.

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REFERENCES

1. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg Infect Dis*. 2006;12(11):1638-1643.

2. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol*. 1998;148(11):1094-1102.

3. Harris JW. Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. *JAMA*. 1919;72(14):978-980. doi:10.1001/jama.1919.02610140008002

4. Greenberg M, Jacobziner H, Pakter J, Weisl BA. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. *Am J Obstet Gynecol*. 1958;76(4):897-902.

5. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. *Am J Obstet Gynecol*. 1959;78:1172-1175.

6. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 Pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. *Am J Obstet Gynecol*. 2011;205(1):10-18.

7. Jamieson DJ, Honein MA, Rasmussen SA, et al; Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet*. 2009;374(9688):451-458.

8. Louie JK, Acosta M, Jamieson DJ, Honein MA; California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med*. 2010;362(1):27-35.

9. Siston AM, Rasmussen SA, Honein MA, et al; Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303(15):1517-1525.

10. Gracie S, Metcalfe A, Dolan SM, Kehler H, Siever J, Tough S. Utilization of the 2009 H1N1 vaccine by pregnant women in a pandemic year. *J Obstet Gynaecol Can*. 2011;33(2):127-133.

11. Centers for Disease Control and Prevention (CDC). Seasonal influenza and 2009 H1N1 influenza vaccination coverage among pregnant women: 10 states, 2009-10 influenza season. *MMWR Morb Mortal Wkly Rep*. 2010;59(47):1541-1545.

12. Tricco AC, Chit A, Soobiah C, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. *BMC Med*. 2013;11:153.

13. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza

vaccines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(1):36-44.

14. Madhi SA, Cutland CL, Kuwanda L, et al; Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med*. 2014;371(10):918-931.

15. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants [published correction appears in *N Engl J Med*. 2009;360(6):648]. *N Engl J Med*. 2008;359(15):1555-1564.

16. Pasternak B, Svanström H, Mølgaard-Nielsen D, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. *BMJ*. 2012;344:e2794.

17. Pasternak B, Svanström H, Mølgaard-Nielsen D, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. *JAMA*. 2012;308(2):165-174.

18. Moro PL, Tepper NK, Grohskopf LA, Vellozzi C, Broder K. Safety of seasonal influenza and influenza A (H1N1) 2009 monovalent vaccines in pregnancy. *Expert Rev Vaccines*. 2012;11(8):911-921.

19. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull*. 1998;45(3):320-323.

20. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7)(suppl):22-25.

21. Grove Krause T, Jakobsen S, Haarh M, Mølbak K. The Danish vaccination register. *Euro Surveill*. 2012;17(17).

22. Statens Serum Institut. Status for influenza-epidemien. http://www.ssi.dk/~/media/Indhold/DK%20-%20dansk/Aktuelt/Nyhedsbreve/EPI-NYT/2009/2009%20PDF/EPI-NYT%20-%202009%20-%20uge%2049.ashx. Accessed November 2, 2016.

23. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253-259.

24. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7)(suppl):30-33.

25. Clayton D, Hills M. *Statistical Models in Epidemiology*. Oxford, England: Oxford University Press; 1993.

26. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol*. 2003;157(4):364-375.

27. Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med*. 2011;165(2):104-111.

28. Ludvigsson JF, Ström P, Lundholm C, et al. Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design. *BMJ*. 2015;351:h5585.

29. van der Maas N, Dijs-Elsinga J, Kemmeren J, van Lier A, Knol M, de Melker H. Safety of vaccination against influenza A (H1N1) during pregnancy in the Netherlands: results on pregnancy outcomes and infant's health: cross-sectional linkage study. *BJOG*. 2016;123(5):709-717.