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Risk of Adverse Fetal Outcomes Following Administration of a Pandemic Influenza A(H1N1) Vaccine During Pregnancy

Björn Pasternak, MD, PhD
Henrik Svanström, MSc
Ditte Mølgaard-Nielsen, MSc
Tyra G. Krause, MD, PhD
Hanne-Dorthe Emborg, DVM
Mads Melbye, MD, DrMedSci
Anders Hviid, MSc, DrMedSci

Context Assessment of the fetal safety of vaccination against influenza A(H1N1) pdm09 in pregnancy has been limited.

Objective To investigate whether exposure to an adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy was associated with increased risk of adverse fetal outcomes.

Design, Setting, and Participants Registry-based cohort study based on all liveborn singleton infants in Denmark, delivered between November 2, 2009, and September 30, 2010. In propensity score–matched analyses, we estimated prevalence odds ratios (PORs) of adverse fetal outcomes, comparing infants exposed and unexposed to an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy.

Main Outcome Measures Major birth defects, preterm birth, and small size for gestational age.

Results From a cohort of 53 432 infants (6989 [13.1%] exposed to the influenza A[H1N1]pdm09 vaccine during pregnancy [345 in the first trimester and 6644 in the second or third trimester]), 660 (330 exposed) were included in propensity score–matched analyses of adverse fetal outcomes associated with first-trimester exposure. For analysis of small size for gestational age after second- or third-trimester exposure, 13 284 (6642 exposed) were included; for analyses of preterm birth, 12 909 (6543 exposed) were included. A major birth defect was diagnosed in 18 of 330 infants (5.5%) exposed to the vaccine in the first trimester, compared with 15 of 330 unexposed infants (4.5%) (POR, 1.21; 95% CI, 0.60-2.45). Preterm birth occurred in 31 of 330 infants (9.4%) exposed in the first trimester, compared with 24 of 330 unexposed infants (7.3%) (POR, 1.32; 95% CI, 0.76-2.31), and in 302 of 6543 infants (4.6%) with second- or third-trimester exposure, compared with 295 of 6366 unexposed infants (4.6%) (POR, 1.00; 95% CI, 0.84-1.17). Small size for gestational age was observed in 25 of 330 infants (7.6%) with first-trimester exposure compared with 31 of 330 unexposed infants (9.4%) (POR, 0.79; 95% CI, 0.46-1.37), and in 641 of 6642 infants (9.7%) with second- or third-trimester exposure, compared with 657 of 6642 unexposed infants (9.9%) (POR, 0.97; 95% CI, 0.87-1.09).

Conclusions In this Danish cohort, exposure to an adjuvanted influenza A(H1N1) pdm09 vaccine during pregnancy was not associated with a significantly increased risk of major birth defects, preterm birth, or fetal growth restriction.

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THE 2009 INFLUENZA A(H1N1) pandemic put pregnant women at increased risk of morbidity, mortality, and poor pregnancy outcomes.[1-4] Pregnant women were among the main target groups prioritized for vaccination against influenza A(H1N1)pdm09,[5] and an estimated 2.4 million women were vaccinated during pregnancy in the United States alone.[6] However, assessment of the fetal safety of H1N1 vaccination in pregnancy has been limited to a few pharmacovigilance reports and descriptive cohort studies.[6-14]

In a registry-based cohort study, we investigated whether exposure to an AS03-adjuvanted influenza A(H1N1) pdm09 vaccine in pregnancy was associated with increased risk of major birth defects, preterm birth, and fetal growth restriction.

For editorial comment see p 184.

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METHODS

We conducted a nationwide registry-based cohort study of liveborn infants in Denmark. Individual-level data on H1N1 vaccination during pregnancy and potential confounders in cohort moth-

Author Affiliations: Departments of Epidemiology Research (Drs Pasternak, Melbye, and Hviid, Mr Svanström and Ms Mølgaard-Nielsen), and Infectious Disease Epidemiology (Drs Krause and Emborg), Statens Serum Institut, Copenhagen, Denmark.
Corresponding Author: Björn Pasternak, MD, PhD, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (bjp@ssi.dk).

ers were linked to the cohort using the unique personal identification number assigned to all inhabitants in Denmark.[15] In propensity score–matched analyses, we investigated associations between H1N1 vaccination in pregnancy and risks of adverse fetal outcomes: major birth defects, preterm birth, and small size for gestational age as the primary outcomes; and secondary outcomes of low birth weight, mean difference in birth weight, and analyses according to categories of preterm birth. We additionally analyzed outcomes in the entire cohort prior to matching, although the propensity score–matched analyses were defined as primary analyses. The study was approved by the Danish Data Protection Agency. In Denmark, ethics approval is not required for registry-based research.

Cohort

On the basis of the Danish Medical Birth Register,[16] we identified a cohort of all liveborn infants in Denmark, delivered between November 2, 2009, and September 30, 2010. The Medical Birth Register contains individual-level information on all deliveries by women living in Denmark, each newborn's date of birth, gestational age, birth weight, and other characteristics, as well as maternal characteristics including parity, body mass index, and smoking status. Gestational age is recorded on the basis of the first day of the last menstrual period; this date is estimated by ultrasonography in most pregnant women. In a study of the use of obstetric ultrasound scanning among pregnant women in Denmark, more than 93% underwent a scan in the year 2000.[17] The onset of pregnancy was defined as the first day of the last menstrual period and was calculated by subtracting gestational age from the date of birth. We excluded multiple births; births with missing gestational age or birth weight; infants 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)[18]; pregnancy onset before February 1, 2009, or after December 31, 2009 (limiting inclusion of participants unlikely to receive the vaccine because pandemic vaccination occurred almost exclusively in November and December),[19] and women vaccinated prior to pregnancy onset. Among mothers who had several births in the study period, only the first was included.

Vaccination

Information on vaccination status was obtained from a national H1N1 vaccination database established by Statens Serum Institut with the purpose of monitoring vaccination coverage, effectiveness, and safety. The only vaccine used in Denmark was the monovalent inactivated AS03-adjuvanted split virion influenza A(H1N1)pdm09 vaccine (Pandemrix, GlaxoSmithKline Biologicals). All health care clinicians administering the pandemic vaccine were mandated by law to report personal identification numbers and dates of vaccination of all vaccinees; reporting was also required for clinicians to receive reimbursement from the Danish National Health Insurance. The database is therefore considered close to complete. The pandemic influenza vaccination campaign in Denmark, starting on November 2, 2009, targeted individuals with chronic diseases, key government personnel, health care personnel, and pregnant women.[20] For pregnant women with chronic diseases, vaccination was recommended in any trimester (in the first trimester after individual assessment). Pregnant women without comorbidities were recommended vaccination in the second and third trimester.

Outcomes

Cases of major birth defects diagnosed until 1 year of age were identified through the Danish National Patient Register,[21] which contains individual-level data on hospital visits and admissions including diagnostic information. Major birth defects were defined according to EUROCAT (a European network for surveillance of congenital anomalies),[22] with minor modifications as described previously.[18] Applying this definition to detect cases from the National Patient Register, the rate of major birth defects in a nationwide cohort of live births in Denmark (2.4%)[18] was similar to the rate reported by EUROCAT for Europe overall (2.1%).[23] Cases of preterm birth (delivery before 37 completed weeks) and small size for gestational age (lowest 10th percentile of the gestational age-specific birth weight within the cohort) were identified on the basis of Medical Birth Register data. Very- and moderately preterm birth were defined as delivery before 32 completed weeks and delivery between the start of week 33 and before 37 completed weeks, respectively. Low birth weight was defined as less than 2500 g, and very low birth weight as less than 1500 g.

Potential Confounders

From the Medical Birth Register, the Danish Central Person Register, the National Patient Register, and the Danish National Prescription Register,[24] we identified potential confounders for inclusion in propensity scores: maternal age, place of birth, degree of urbanization at place of living, parity, smoking status, and prepregnancy body mass index; history of any birth defects, preterm birth, spontaneous abortion, and small size for gestational age; maternal comorbidities and use of drugs (eTable 1 available at http://www.jama.com); and health care utilization: number of hospital admissions and hospital outpatient visits in the last 3 years, and number of drugs used in the last 6 months. We had no data on comorbidities diagnosed exclusively in the primary care setting, inpatient drug treatment, alcohol use, over-the-counter medications, or vitamin supplements.

Statistical Analyses

For the outcome of major birth defects, the exposure time window com-

prised the first trimester (pregnancy onset through 12 gestational weeks). For all other outcomes, we aimed to analyze risks associated with exposure throughout pregnancy. Because only women with comorbidities had indication for vaccination in the first trimester, we expected that characteristics of mothers vaccinated in this time period would differ from that of mothers vaccinated in the second or third trimester. Because we also expected that the number of those exposed in the first trimester would be small, we anticipated that the comorbidity status of these mothers would not be captured adequately by a propensity score common for the entirety of pregnancy. We therefore separated the analyses into 2 exposure time windows: vaccination in the first trimester and vaccination in the second or third trimester. Those exposed in the first trimester were excluded from analyses of the second- or third-trimester time window.

In the analyses, pregnancies contributed to follow-up from the first day of the vaccination campaign (November 2, 2009), in order for all contributing pregnancies to be at risk of vaccination. To be eligible for the analysis of a distinct exposure time window, participants were required to have follow-up during this specific time window. For example, a participant with pregnancy onset on July 1, 2009, did not start contributing follow-up to the cohort until November 2, 2009; hence, the participant did not have follow-up in the first trimester and was not eligible for the analysis of birth defects, in which pregnancies had to have follow-up in the first trimester. Additionally, participants included in the analysis of preterm birth were required to have had follow-up before 37 completed gestational weeks; else they were excluded from this analysis.

A propensity score for each participant was estimated using logistic regression as the predicted probability of vaccination conditional on all potential confounders listed previously. Additionally, all 2-way interactions between potential confounders, except for maternal comorbidities and medications, were included in the propensity scores. We used mode imputation for variables with missing values. Distinct propensity scores were estimated for first-trimester exposure and for second- or third-trimester exposure. After estimation of propensity scores, exposed and unexposed participants in each exposure time window were matched 1:1 (greedy matching) on the second decimal of the propensity score. Participants with no match were excluded from the propensity score–matched analyses.

Logistic regression was used to estimate prevalence odds ratios (PORs) with 95% CIs comparing prevalence odds of adverse fetal outcomes in the unmatched cohorts and in propensity score–matched cohorts of infants from vaccinated and unvaccinated pregnancies.[25] For the analysis of mean difference in birth weight associated with vaccination in pregnancy, normal linear regression was used. In preplanned sensitivity analyses, we estimated birth defect risk associated with vaccination in the period of maximal susceptibility to teratogenic agents, 4 to 10 gestational weeks (corresponding to 2-8 weeks after estimated conception)[26]; estimated risks of adverse outcomes according to maternal comorbidity status in which comorbidity was defined as any of the diagnoses listed in TABLE 1 with the exception of disorder of female pelvic organ/genital tract and hospital contact for injury and poisoning; and estimated the risk of small size for gestational age by trimester of vaccination. Posthoc, estimates for primary outcomes were additionally adjusted for exposure to seasonal influenza vaccine (data on seasonal influenza vaccination [recommended only for pregnant women with chronic diseases] were obtained from the National Board of Health; reporting of seasonal influenza vaccination was not mandatory but necessary for cost reimbursement). A difference between groups was considered statistically significant if the 95% CI did not overlap 1.0 in either direction. SAS software (version 9.2) was used for all analyses.

RESULTS

Study Cohort

FIGURE 1 illustrates the enrollment of participants in the cohort. Following exclusions, a cohort of 53 432 liveborn infants was identified with 6989 (13.1%) exposed to the influenza A(H1N1)pdm09 vaccine during pregnancy. Most were exposed to the vaccine in November 2009 (FIGURE 2); the median gestational age at the time of vaccination was 174 days (range, 0-285 days; ie, 24 weeks, 6 days). In the unmatched cohort, 345 vaccine-exposed and 22 917 unexposed participants were included in analyses of first-trimester exposure; correspondingly, there were 6644 exposed and 46 443 unexposed in analyses of second- or third-trimester exposure (Figure 1). Participants exposed in the first trimester were older, more often had a history of adverse pregnancy outcomes, had higher body mass index, were more often smokers, had higher prevalence of several comorbidities such as respiratory disease and diabetes, were more often users of prescription medications such as antidepressants and analgetics, and had more health care utilization (Table 1; TABLE 2). Although there were some differences in the distribution of baseline characteristics such as age between participants exposed and unexposed in the second or third trimester, these 2 groups were more similar (Table 1; Table 2). The C-statistic (an estimate of the ability of the propensity score model to predict vaccination status) was 0.81 for first-trimester exposure and 0.62 for second- or third-trimester exposure. After 1:1 propensity score matching, 660 (330 exposed) infants were included in analyses of adverse fetal outcomes associated with vaccination in the first trimester, and 13 284 (6642 exposed) in analyses of adverse fetal outcomes associated with vaccination in the second or

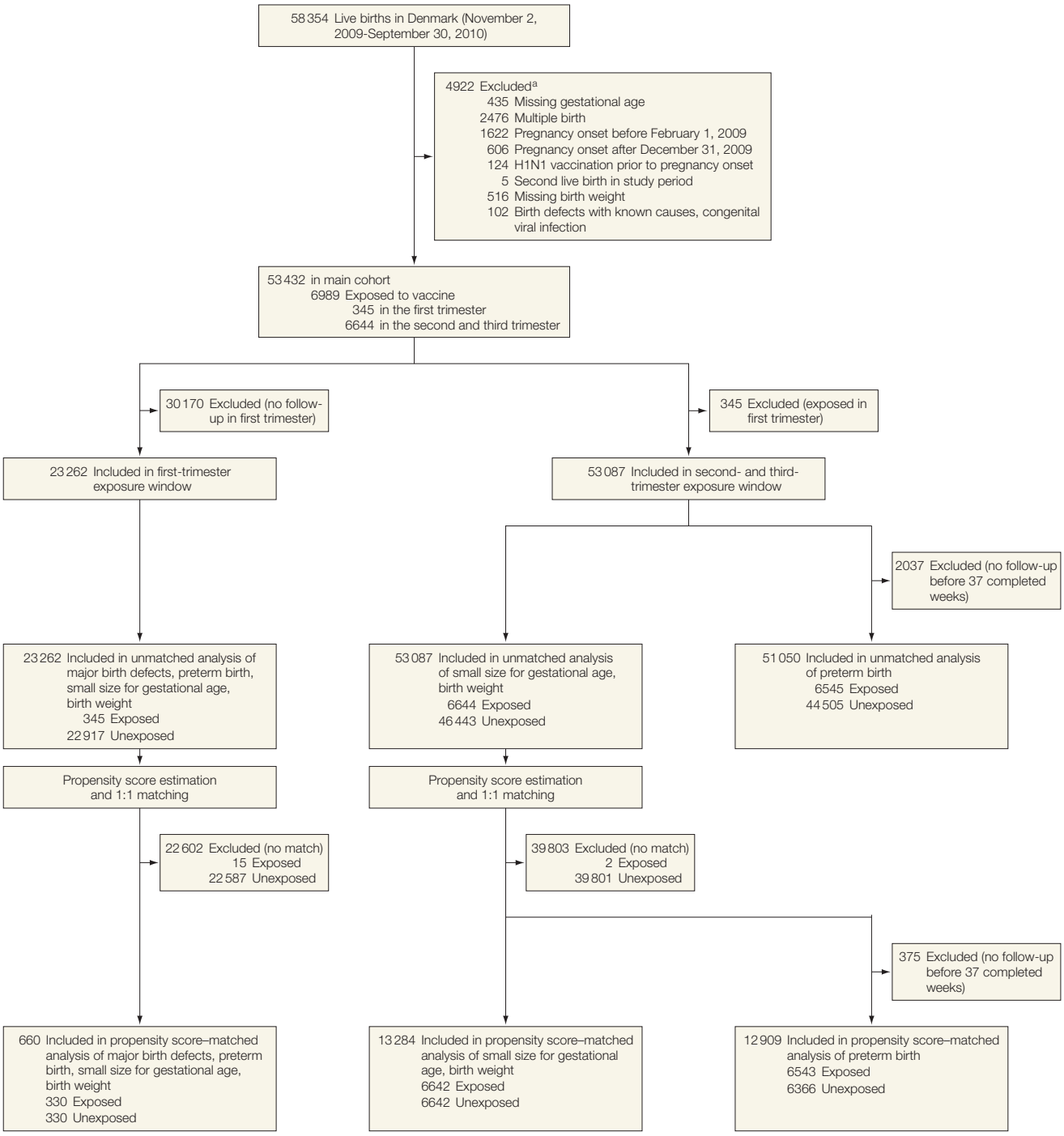
Table 1. Demographics and Pregnancy History in Mothers Exposed and Unexposed to Influenza A(H1N1)pdm09 Vaccine During Pregnancy[a]

	Time Window of Exposure to Vaccine, No. (%)							
	First Trimester				Second or Third Trimester			
	Unmatched Cohort		Propensity Score–Matched Cohort[b]		Unmatched Cohort		Propensity Score–Matched Cohort[b]	
Characteristic	Unexposed (n = 22 917)	Exposed (n = 345)	Unexposed (n = 330)	Exposed (n = 330)	Unexposed (n = 46 443)	Exposed (n = 6644)	Unexposed (n = 6642)	Exposed (n = 6642)
Age at pregnancy onset, mean (SD), y	30.1 (5.0)	30.7 (5.2)	30.4 (5.4)	30.5 (5.1)	30.0 (5.0)	30.9 (4.7)	30.7 (4.9)	30.9 (4.7)
Age group, y								
<25	3642 (16)	49 (14)	54 (16)	49 (15)	7472 (16)	727 (11)	751 (11)	727 (11)
25-34	15 592 (68)	223 (65)	201 (61)	218 (66)	31 613 (68)	4643 (70)	4592 (69)	4641 (70)
≥35	3683 (16)	73 (21)	75 (23)	63 (19)	7358 (16)	1274 (19)	1299 (20)	1274 (19)
Residential degree of urbanization								
Copenhagen	4057 (18)	72 (21)	68 (21)	72 (22)	8095 (17)	1329 (20)	1321 (20)	1327 (20)
Copenhagen suburbs	4382 (19)	66 (19)	64 (19)	61 (18)	8794 (19)	1334 (20)	1412 (21)	1334 (20)
Population density ≥200 inhabitants/km^2	2596 (11)	48 (14)	36 (11)	43 (13)	5038 (11)	867 (13)	875 (13)	867 (13)
Population density 100-199 inhabitants/km^2	4693 (20)	65 (19)	67 (20)	63 (19)	9573 (21)	1241 (19)	1219 (18)	1241 (19)
Population density 50-99 inhabitants/km^2	6074 (27)	78 (23)	72 (22)	77 (23)	12 607 (27)	1596 (24)	1551 (23)	1596 (24)
Population density ≤49 inhabitants/km^2	1115 (5)	16 (5)	23 (7)	14 (4)	2336 (5)	277 (4)	264 (4)	277 (4)
Place of birth								
Denmark	19 322 (84)	288 (83)	269 (82)	279 (85)	38 834 (84)	5691 (86)	5667 (85)	5690 (86)
Europe	1004 (4)	16 (5)	15 (5)	16 (5)	2093 (5)	310 (5)	310 (5)	309 (5)
Other	2591 (11)	41 (12)	46 (14)	35 (11)	5516 (12)	643 (10)	665 (10)	643 (10)
Month of pregnancy onset[c]								
February	NA	NA	NA	NA	3421 (7)	399 (6)	497 (7)	399 (6)
March	NA	NA	NA	NA	3747 (8)	1022 (15)	516 (8)	1022 (15)
April	NA	NA	NA	NA	3812 (8)	1090 (16)	548 (8)	1090 (16)
May	NA	NA	NA	NA	3995 (9)	1287 (19)	527 (8)	1286 (19)
June	NA	NA	NA	NA	3814 (8)	1130 (17)	527 (8)	1129 (17)
July	NA	NA	NA	NA	3877 (8)	979 (15)	566 (9)	979 (15)
August	3501 (15)	68 (20)	53 (16)	67 (20)	4462 (10)	636 (10)	632 (10)	636 (10)
September	5027 (22)	136 (39)	67 (20)	132 (40)	4938 (11)	89 (1)	743 (11)	89 (1)
October	5394 (24)	94 (27)	75 (23)	87 (26)	5385 (12)	9 (<1)	744 (11)	9 (<1)
November	5059 (22)	47 (14)	78 (24)	44 (13)	5056 (11)	3 (<1)	769 (12)	3 (<1)
December	3936 (17)	0	57 (17)	0	3936 (8)	0	573 (9)	0
Pregnancy history								
Parity								
0	10 134 (44)	140 (41)	133 (40)	139 (42)	20 852 (45)	2603 (39)	2629 (40)	2603 (39)
1	8542 (37)	147 (43)	141 (43)	142 (43)	16 902 (36)	2747 (41)	2723 (41)	2745 (41)
2	3202 (14)	36 (10)	36 (11)	34 (10)	6531 (14)	994 (15)	978 (15)	994 (15)
≥3	1039 (5)	22 (6)	20 (6)	15 (5)	2158 (5)	300 (5)	312 (5)	300 (5)
Adverse pregnancy outcomes								
Spontaneous abortion	3629 (16)	70 (20)	66 (20)	66 (20)	6215 (13)	924 (14)	915 (14)	924 (14)
Preterm birth	909 (4)	21 (6)	24 (7)	18 (5)	1755 (4)	298 (4)	286 (4)	297 (4)
Small size for gestational age	1714 (7)	29 (8)	30 (9)	26 (8)	3557 (8)	522 (8)	546 (8)	521 (8)
Any birth defect	1191 (5)	23 (7)	19 (6)	18 (5)	2253 (5)	426 (6)	412 (6)	426 (6)
BMI at pregnancy onset[d]								
<18.5	1516 (7)	26 (8)	30 (9)	22 (7)	3042 (7)	424 (6)	421 (6)	423 (6)
18.5-24	14 051 (61)	177 (51)	172 (52)	173 (52)	28 508 (61)	4001 (60)	4019 (61)	4001 (60)
25-29	4596 (20)	83 (24)	73 (22)	80 (24)	9394 (20)	1342 (20)	1354 (20)	1341 (20)
30-34	1816 (8)	31 (9)	30 (9)	29 (9)	3645 (8)	505 (8)	503 (8)	505 (8)
≥35	938 (4)	28 (8)	25 (8)	26 (8)	1854 (4)	372 (6)	345 (5)	372 (6)
Smoking at pregnancy onset	2790 (12)	50 (14)	56 (17)	46 (14)	5952 (13)	755 (11)	761 (11)	755 (11)

Abbreviations: BMI, body mass index; NA, not applicable.
[a] Nationwide cohort of liveborn infants and their mothers in Denmark. The cohort was divided into 2 exposure time windows. All values are shown as No. (%) unless otherwise stated. Characteristics are described as current at pregnancy onset, unless stated otherwise. Because of rounding, percentages may not total 100.
[b] Matched 1:1 on the propensity score.
[c] All months of pregnancy onset are in 2009.
[d] BMI is calculated as weight in kilograms divided by height in meters squared.

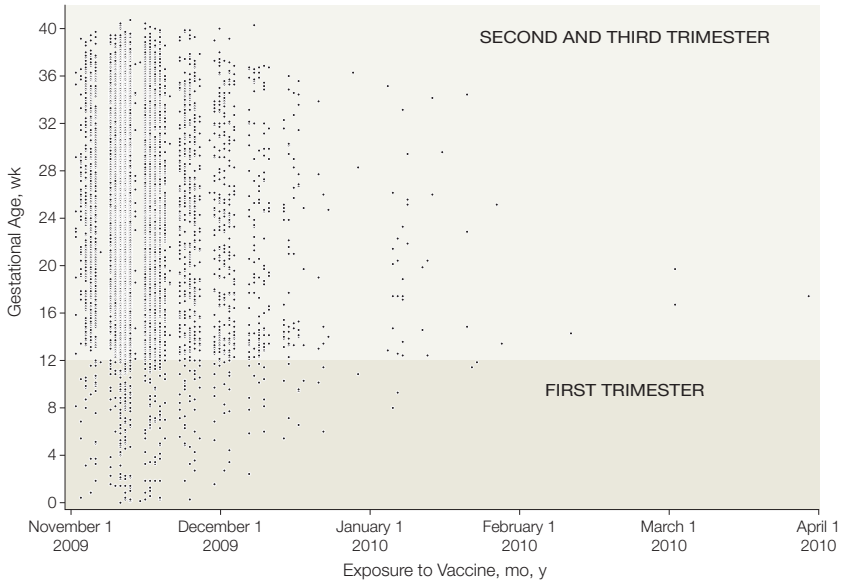
third trimester (Figure 1). The analysis of preterm birth associated with exposure in the second or third trimester was based on 6543 exposed and 6366 unexposed infants, as those without follow-up before 37 completed weeks of gestation were excluded (Figure 1). Exposed and unexposed participants included in analyses of first-trimester exposure were reasonably well balanced with respect to baseline characteristics

Figure 1. Enrollment of Participants in the Cohort and Setup of the Analyses



[a] Values will not sum because some live births were excluded for more than 1 of the categorized reasons.

Figure 2. Gestational Age at the Time of Exposure to Influenza A(H1N1)pdm09 Vaccine by Date of Vaccination



In November and early December, days when very few vaccinations were administered are weekend days and appear as empty columns.

included in the propensity score, although there were smaller differences between the groups; participants included in analyses of second- or third-trimester exposure were well balanced (Table 1; Table 2).

Unmatched Cohort Analyses

In the unmatched analyses, participants with first-trimester exposure to the vaccine, when compared with the unexposed, had higher prevalences of major birth defects and preterm birth but not low birth weight and small size for gestational age (TABLE 3). Correspondingly, the PORs for the associations between vaccine exposure and major birth defects and preterm birth, respectively, were significantly increased (Table 3). Vaccination in the first trimester was not associated with a difference in birth weight (mean difference, –49 g; 95% CI, –108 to 10). Participants exposed to the vaccine in the second or third trimester did not have higher prevalences of any of the outcomes when compared with the unexposed; the PORs were not significantly increased for any outcome (Table 3). Similarly, vaccination was not associated with a difference in birth weight (mean difference, –2; 95% CI, –16 to 12).

Propensity Score–Matched Analyses

There were 18 infants (5.5%) diagnosed with a major birth defect among those exposed to the vaccine in the first trimester of pregnancy compared with 15 (4.5%) among the unexposed (POR, 1.21; 95% CI, 0.60-2.45; Table 3). No infant was diagnosed with more than major birth defect and no unexpected cluster of specific birth defects was observed; birth defect diagnoses in the 2 groups are listed in eTable 2.

Among infants exposed to the H1N1 vaccine in the first trimester, 31 (9.4%) were born preterm compared with 24 (7.3%) among the unexposed (POR, 1.32; 95% CI, 0.76-2.31; Table 3). There was no increased risk of preterm birth associated with H1N1 vaccination in the second or third trimester (302 [4.6%] exposed vs 295 [4.6%] unexposed; POR, 1.00; 95% CI, 0.84-1.17; Table 3). When analyzed according to category of preterm birth, there was no increased risk of moderately and very preterm birth associated with vaccination in the second or third trimester (Table 3).

There was no increased risk of low birth weight associated with vaccination in the first trimester (15 [4.5%] exposed vs 18 [5.5%] unexposed; POR, 0.83; 95% CI, 0.41-1.67; Table 3) and no increased risk of low birth weight (225 [3.4%] exposed vs 199 [3.0%] unexposed; POR, 1.14; 95% CI, 0.94-1.38) or very low birth weight associated with vaccination in the second or third trimester (Table 3). Vaccination was not associated with a difference in birth weight (mean difference, 18 g; 95% CI, –70 to 106 for first-trimester exposure; mean difference, –4 g; 95% CI, –23 to 15 for second- or third-trimester exposure). Taking gestational age into account, there was no increased risk of small size for gestational age associated with vaccination in the first (25 [7.6%] exposed vs 31 [9.4%] unexposed; POR, 0.79; 95% CI, 0.46-1.37) or the second or third trimester (641 [9.7%] exposed vs 657 [9.9%] unexposed; POR, 0.97; 95% CI, 0.87-1.09; Table 3).

Sensitivity Analyses

The POR for major birth defects associated with vaccination in the period of maximal susceptibility to teratogenic agents (4 to 10 gestational weeks) was similar to that in the main analysis (TABLE 4). In analyses according to maternal comorbidity status, the PORs for the associations between first-trimester exposure and major birth defects, second- or third-trimester exposure and preterm birth, and second- or third-trimester exposure and small size for gestational age were all similar in infants with mothers with or without comorbidities (Table 4). Because fetal growth restriction develops over some period of time, our initial analysis of small size for gestational age, which combined exposures in the second and third trimester, might not have adequately captured a risk associated with vaccination; however, when this expo-

sure time window was split by trimester, PORs for second- and third-trimester exposure, respectively, were similar (Table 4). Overall, PORs for preterm birth and small size for gestational age associated with H1N1 vaccination in the second or third trimester did not change when adjusted for exposure to seasonal influenza vaccine (Table 4).

COMMENT

In propensity score–matched analyses, this cohort study found no significant associations between exposure to an AS03-adjuvanted influenza A(H1N1)

Table 2. Comorbidities, Medications, and Health Care Utilization in Mothers Exposed and Unexposed to Influenza A(H1N1)pdm09 Vaccine During Pregnancy[a]

	Time Window of Exposure to Vaccine, No. (%)							
	First Trimester				Second or Third Trimester			
	Unmatched Cohort		Propensity Score–Matched Cohort[b]		Unmatched Cohort		Propensity Score–Matched Cohort[b]	
Characteristic	Unexposed (n = 22 917)	Exposed (n = 345)	Unexposed (n = 330)	Exposed (n = 330)	Unexposed (n = 46 443)	Exposed (n = 6644)	Unexposed (n = 6642)	Exposed (n = 6642)
Comorbidities and medications[c]								
Pulmonary disease/antiobstructive inhalants	901 (4)	63 (18)	53 (16)	54 (16)	1709 (4)	399 (6)	394 (6)	398 (6)
Cardiovascular disease/cardiovascular drugs	637 (3)	21 (6)	24 (7)	17 (5)	1186 (3)	253 (4)	251 (4)	252 (4)
Hematological disease	199 (1)	5 (1)	4 (1)	5 (2)	392 (1)	88 (1)	77 (1)	87 (1)
Diabetes/antidiabetic drugs	378 (2)	21 (6)	11 (3)	20 (6)	699 (2)	165 (2)	173 (3)	164 (2)
Neurological disease	488 (2)	19 (6)	27 (8)	17 (5)	1029 (2)	195 (3)	186 (3)	194 (3)
Liver and kidney disease	129 (1)	2 (1)	1 (<1)	2 (1)	267 (1)	52 (1)	57 (1)	51 (1)
Rheumatic disease	106 (<1)	7 (2)	5 (2)	6 (2)	228 (<1)	51 (1)	49 (1)	50 (1)
Inflammatory bowel disease/intestinal anti-inflammatory agents	195 (1)	12 (3)	9 (3)	10 (3)	414 (1)	79 (1)	68 (1)	79 (1)
Obesity	1145 (5)	24 (7)	35 (11)	23 (7)	2252 (5)	372 (6)	351 (5)	372 (6)
Immunodefiency/immunosuppressants	31 (<1)	5 (1)	2 (1)	3 (1)	66 (<1)	23 (<1)	20 (<1)	22 (<1)
Disorders of female pelvic organs/genital tract	2652 (12)	59 (17)	61 (18)	57 (17)	5336 (11)	874 (13)	842 (13)	873 (13)
Hospital contact for injury or poisoning	4979 (22)	95 (28)	102 (31)	86 (26)	10 118 (22)	1388 (21)	1384 (21)	1386 (21)
Antidepressants	1097 (5)	27 (8)	24 (7)	25 (8)	2146 (5)	378 (6)	376 (6)	378 (6)
Antiepileptics	169 (1)	2 (1)	4 (1)	2 (1)	275 (1)	45 (1)	50 (1)	45 (1)
Drugs for peptic ulcer/gastroesophageal reflux	609 (3)	19 (6)	17 (5)	17 (5)	1203 (3)	219 (3)	220 (3)	218 (3)
Contraceptive pills	5557 (24)	74 (21)	60 (18)	72 (22)	10 847 (23)	1424 (21)	1426 (21)	1424 (21)
Drugs for in vitro fertilization	1639 (7)	31 (9)	36 (11)	31 (9)	3144 (7)	517 (8)	524 (8)	517 (8)
Thyroid hormones	216 (1)	5 (1)	8 (2)	4 (1)	465 (1)	89 (1)	95 (1)	89 (1)
Systemic corticosteroids	331 (1)	12 (3)	7 (2)	10 (3)	569 (1)	114 (2)	120 (2)	112 (2)
NSAIDs	1867 (8)	36 (10)	34 (10)	32 (10)	3823 (8)	608 (9)	624 (9)	608 (9)
Opiates	465 (2)	20 (6)	23 (7)	16 (5)	897 (2)	152 (2)	157 (2)	152 (2)
Systemic antibacterial agents	4803 (21)	91 (26)	83 (25)	85 (26)	10 355 (22)	1683 (25)	1664 (25)	1681 (25)
Seasonal influenza vaccine[d]	25 (<1)	21 (6)	0	19 (6)	27 (<1)	38 (1)	3 (<1)	38 (1)
Health care utilization								
Hospital admissions in the last 3 years								
0	11 089 (48)	144 (42)	146 (44)	141 (43)	22 749 (49)	2939 (44)	2961 (45)	2939 (44)
1-2	10 047 (44)	157 (46)	149 (45)	149 (45)	20 186 (43)	3121 (47)	3119 (47)	3120 (47)
3-4	1360 (6)	28 (8)	23 (7)	25 (8)	2706 (6)	437 (7)	433 (7)	436 (7)
≥5	421 (2)	16 (5)	12 (4)	15 (5)	802 (2)	147 (2)	129 (2)	147 (2)
Outpatient hospital contacts in the last 3 years								
0	7321 (32)	76 (22)	73 (22)	74 (22)	15 014 (32)	1917 (29)	1974 (30)	1917 (29)
1-2	8645 (38)	121 (35)	128 (39)	120 (36)	17 588 (38)	2480 (37)	2499 (38)	2480 (37)
3-4	4321 (19)	67 (19)	53 (16)	67 (20)	8671 (19)	1319 (20)	1282 (19)	1319 (20)
≥5	2630 (11)	81 (23)	76 (23)	69 (21)	5170 (11)	928 (14)	887 (13)	926 (14)
Drugs used in the last 6 months								
0	7434 (32)	63 (18)	71 (22)	63 (19)	15 475 (33)	1892 (28)	1874 (28)	1892 (28)
1-2	10 040 (44)	137 (40)	119 (36)	134 (41)	20 184 (43)	2868 (43)	2882 (43)	2868 (43)
3-4	3587 (16)	88 (26)	82 (25)	81 (25)	7186 (15)	1166 (18)	1156 (17)	1166 (18)
≥5	1856 (8)	57 (17)	58 (18)	52 (16)	3598 (8)	718 (11)	730 (11)	716 (11)

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Nationwide cohort of liveborn infants and their mothers in Denmark. The cohort was divided into 2 exposure time windows. Characteristics are described as current at pregnancy onset, unless stated otherwise. Because of rounding, percentages may not total 100.
[b] Matched 1:1 on the propensity score.
[c] Comorbidities as registered in the least 3 years, and medication as registered in the last 6 months.
[d] Exposure within respective time window during pregnancy.

pdm09 vaccine in pregnancy and adverse fetal outcomes including major birth defects, preterm birth, and fetal growth restriction. The analyses of adverse fetal outcomes associated with vaccination in the second or third trimester of pregnancy were based on more than 6600 exposed infants, and the data provide robust evidence of

Table 3. Association Between Vaccination Against Influenza A(H1N1)pdm09 in Pregnancy and Risk of Adverse Fetal Outcomes, Nationwide Cohort of Liveborn Infants in Denmark

	Unmatched Cohort Analysis			Propensity Score–Matched Analysis		
	Cases, No. (%)			Cases, No. (%)		
Outcome	Unexposed	Exposed	Unadjusted POR (95% CI)	Unexposed	Exposed	POR (95% CI)
Vaccination in first trimester	**n = 22 917**	**n = 345**		**n = 330**	**n = 330**	
Major birth defects	545 (2.4)	18 (5.2)	2.26 (1.40-3.66)	15 (4.5)	18 (5.5)	1.21 (0.60-2.45)
Preterm birth[a]	1109 (4.8)	33 (9.6)	2.08 (1.45-2.99)	24 (7.3)	31 (9.4)	1.32 (0.76-2.31)
Low birth weight[b]	781 (3.4)	15 (4.3)	1.29 (0.76-2.17)	18 (5.5)	15 (4.5)	0.83 (0.41-1.67)
Small size for gestational age[c]	2268 (9.9)	25 (7.2)	0.71 (0.47-1.07)	31 (9.4)	25 (7.6)	0.79 (0.46-1.37)
Vaccination in second or third trimester	**n = 46 443[d]**	**n = 6644[d]**		**n = 6642[e]**	**n = 6642[e]**	
Preterm birth[a]	2055 (4.6)	303 (4.6)	1.00 (0.89-1.13)	295 (4.6)	302 (4.6)	1.00 (0.84-1.17)
Moderately preterm	1803 (4.1)	265 (4.0)	1.00 (0.88-1.14)	257 (4.0)	264 (4.0)	1.00 (0.84-1.19)
Very preterm	252 (0.6)	38 (0.6)	1.03 (0.73-1.44)	38 (0.6)	38 (0.6)	0.97 (0.63-1.53)
Low birth weight[b]						
Low	1433 (3.1)	225 (3.4)	1.10 (0.95-1.27)	199 (3.0)	225 (3.4)	1.14 (0.94-1.38)
Very low	210 (0.5)	32 (0.5)	1.07 (0.74-1.55)	29 (0.4)	32 (0.5)	1.11 (0.67-1.83)
Small size for gestational age[c]	4620 (9.9)	641 (9.6)	0.97 (0.89-1.05)	657 (9.9)	641 (9.7)	0.97 (0.87-1.09)

Abbreviation: POR, prevalence odds ratio.
[a] Preterm birth was defined as delivery prior to 37 completed weeks, moderately preterm as between the start of week 33 and prior to 37 completed weeks, and very preterm as less than 32 completed weeks.
[b] Low birth weight was defined as birth weight below 2500 g and very low birth weight below 1500 g.
[c] Small size for gestational age was defined as the lowest 10th percentile of the gestational age-specific birth weight within the cohort.
[d] The analysis of preterm birth in the unmatched cohort analysis of second- or third-trimester exposure was based on 44 505 unexposed and 6545 exposed participants.
[e] The analysis of preterm birth in the propensity score–matched analysis of second- or third-trimester exposure was based on 6366 unexposed and 6543 exposed participants.

Table 4. Sensitivity Analyses of Associations Between Vaccination Against Influenza A(H1N1)pdm09 in Pregnancy and Adverse Fetal Outcomes

	No. (%)				
	Unexposed		Exposed		
Analysis	Participants	Cases	Participants	Cases	POR (95% CI)[a]
Major birth defects, alternative exposure time window					
Vaccination in gestational weeks 4 to 10	330	15 (4.5)	215	12 (5.6)	1.24 (0.57-2.71)
Adverse fetal outcomes according to comorbidity status[b]					
Major birth defects[c]					
Comorbidity	135	9 (6.7)	126	8 (6.3)	0.95 (0.35-2.54)
No comorbidity	195	6 (3.1)	204	10 (4.9)	1.62 (0.58-4.56)
Preterm birth[d]					
Comorbidity	1294	73 (5.6)	1374	96 (7.0)	1.26 (0.92-1.72)
No comorbidity	5072	222 (4.4)	5169	206 (4.0)	0.91 (0.75-1.10)
Small size for gestational age[d]					
Comorbidity	1352	135 (10.0)	1389	148 (10.7)	1.08 (0.84-1.38)
No comorbidity	5290	522 (9.9)	5253	493 (9.4)	0.95 (0.83-1.08)
Small size for gestational age, according to trimester of vaccination					
Second	6642	657 (9.9)	3528	316 (9.0)	0.90 (0.78-1.03)
Third	6642	657 (9.9)	3114	325 (10.4)	1.06 (0.92-1.22)
Adjusted for exposure to seasonal influenza vaccine[d,e]					
Preterm birth	6366	295 (4.6)	6543	302 (4.6)	0.99 (0.84-1.17)
Small size for gestational age	6642	657 (9.9)	6642	641 (9.7)	0.97 (0.86-1.09)

Abbreviation: POR, prevalence odds ratio.
[a] Values are based on propensity score–matched analyses.
[b] Comorbidity status is based on having a comorbidity if registered with any of the diagnoses listed in Table 2, with the exception of diagnoses of disorder of female pelvic organ/genital tract and hospital contact for injury and poisoning.
[c] First-trimester exposure time window.
[d] Second- or third-trimester exposure time window.
[e] Because no unexposed participants had exposure to seasonal influenza vaccine in the first trimester (Table 2), PORs could not be calculated for this time window.

safety with high precision; results were similar in both unmatched and propensity score–matched analyses. However, vaccination in the first trimester was uncommon and the participants exposed in the first trimester were a high-risk population with more than double the rate of major birth defects and preterm birth than the unexposed in the unmatched population. Nevertheless, relative to a matched comparison group, no significant associations between vaccine exposure in the first trimester and adverse outcomes were observed, although the data only allow the exclusion of large risks of birth defects and preterm birth and a moderate risk of small size for gestational age.

Among the limited number of previous reports on the fetal safety of H1N1 vaccination in pregnancy, which have included both adjuvanted and nonadjuvanted vaccines, no study has directly compared fetal outcomes from vaccinated and unvaccinated pregnancies. Pharmacovigilance reports have not identified safety concerns linked to vaccination in pregnancy[6-10]; however, such studies cannot exclude risks with certainty. The few cohort studies that have been conducted have not identified increased risks of birth defects, preterm birth, or fetal growth restriction associated with vaccination against influenza A(H1N1)pdm09 in pregnancy[11-14]; for example, a prospective cohort study of 267 women exposed to the AS03-adjuvanted H1N1 vaccine reported that the rates of birth defects, preterm birth, and low birth weight were not higher than expected.[11] However, these studies failed to include unexposed control participants, did not present adequate estimates of risk, were underpowered, and collectively included 64 infants exposed in the first trimester and around 1000 infants exposed at any time during pregnancy with available follow-up data at birth. Therefore, they cannot be considered as providing evidence of safety. Thus, our report expands on the limited previous data investigating adverse fetal outcomes associated with H1N1 vaccination in pregnancy; it provides results from a large cohort study with a comparative analytical design. Together with our findings of no significantly increased risk of spontaneous abortion and stillbirth associated with vaccination,[27] these data provide reassurance of the safety of the AS03-adjuvanted A(H1N1) pdm09 vaccine in pregnancy. Our data might be generalizable to nonadjuvanted A(H1N1)pdm09 vaccines because they contain identical viral antigens, although the antigen doses and manufacturing processes may differ. However, results from this study do not provide evidence of safety for vaccines with other adjuvants. Additionally, our study adds to the body of safety data for seasonal influenza vaccines, which rests on a limited number of comparative studies and few studies investigating, eg, birth defect risk.[28,29] Apart from providing information on influenza A(H1N1)pdm09 vaccine safety in pregnancy in retrospect, studies such as ours may have implications for future influenza seasons and pandemics; in some circumstances, the use of adjuvanted vaccines will likely be critical to achieve sufficient host immune responses.[30]

Our study had strengths and limitations. The registry-based study design allowed nationwide coverage and independent ascertainment of exposure and outcomes. We took into account many potential confounders but identification of maternal comorbidity, for example gestational diabetes, was incomplete because the National Patient Register is restricted to the hospital setting. Conversely, many drugs were included as potential confounders, and because the National Prescription Register covers all dispensed prescriptions in the country, drug use may have served as a useful proxy for comorbidity. Because women with comorbidities likely represented the majority of participants vaccinated in the first trimester, it is possible that results for this exposure time window were biased toward increased risk. Only women with comorbidities had indication for vaccination in the first trimester (although some who were health care or key government personnel and pregnant were likely also vaccinated in this time period). Therefore, the population exposed in the first trimester had a higher prevalence of factors that influence the risk of adverse fetal events. Indeed, the rates of major birth defects and preterm birth in this group were twice the rate in the general Danish population.[18,31] Nonetheless, although participants exposed in the first trimester represented a high-risk population, when compared with an unexposed group matched on a wide range of characteristics, the vaccinated group was not at significantly increased risk of adverse fetal events. However, given these limitations and also the low power for the first-trimester exposure time window, the results for adverse outcomes associated with first-trimester exposure should be viewed as preliminary and in need of confirmation.

We cannot exclude the possibility that the relatively small proportion of women (13%) who were vaccinated against pandemic influenza had some unmeasured characteristics that were different when compared with the unexposed. If such factors were associated with lower adverse fetal outcome risks, for example folate use and birth defect risk, they could have obscured fetal risks associated with vaccination. Our study did not include abortions or stillbirths. If vaccine-induced adverse fetal outcomes were simultaneously associated with abortion or stillbirth, results of the study would have been biased toward the null. However, in our previous study, H1N1 vaccination in pregnancy was not associated with increased risk of spontaneous abortion or stillbirth.[27] The low vaccination coverage in the present study (13%), which contrasts to some countries but is similar to others,[32-34] is probably explained by the fact that the 2009/2010 season was the first time that all pregnant women were recommended to receive influenza vaccination in Denmark; for example, in the United States (coverage 40%)[32] all pregnant women have been recommended vaccination

since 2004.[35] Lastly, when interpreting results of the current study, it is important to note that it was designed to investigate safety, not effectiveness. Therefore, it did not address the question of whether maternal vaccination is associated with fetal benefits.

In conclusion, this nationwide cohort study in Denmark found no significant associations between exposure to an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine in pregnancy and risk of adverse fetal outcomes including major birth defects, preterm birth, and growth restriction. Although the data provide robust evidence of safety with respect to outcomes associated with second- or third-trimester exposure, results from analyses of first-trimester exposure should be viewed as preliminary and need confirmation. Further research also needs to address risk of specific birth defects as well as effectiveness of H1N1 vaccination in pregnancy.

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Study concept and design: Pasternak, Svanström, Mølgaard-Nielsen, Hviid.
Acquisition of data: Svanström, Krause, Emborg, Hviid.
Analysis and interpretation of data: Pasternak, Svanström, Mølgaard-Nielsen, Krause, Emborg, Melbye, Hviid.
Drafting of the manuscript: Pasternak.
Critical revision of the manuscript for important intellectual content: Svanström, Mølgaard-Nielsen, Krause, Emborg, Melbye, Hviid.
Statistical analysis: Svanström.
Obtained funding: Pasternak.
Study supervision: Krause, Melbye, Hviid.
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Online-Only Material: eTable 1, eTable 2, and the Author Video Interview are available at http://www.jama.com.

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