Maternal vaccination against H1N1 influenza and offspring mortality – population based cohort study and sibling design

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JFL conceived and designed the study with input from the other authors. JFL also wrote the first draft of the paper and supervised the project. JFL and SC funded the study. PS analyzed the data, with support from CL and FG. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version. JFL is the guarantor of this paper.

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Data sharing
Other researchers can apply for our data through the Swedish National Board of Health and Welfare

Transparency
The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Several studies have reported a neutral relationship between maternal H1N1 vaccination during pregnancy and risk of adverse fetal outcome, but data on longterm mortality in offspring are missing.
- Lack of adjustment for residual confounding (genetic and environmental) shared within families is a potential source of bias in earlier studies.

WHAT THIS STUDY ADDS

- H1N1 vaccination during pregnancy does not seem to influence offspring mortality after the neonatal period.
- We confirm a neutral association between H1N1 vaccination during pregnancy and adverse fetal outcome, also when intrafamilial factors are taken into account.

Running head: H1N1 vaccination and offspring mortality

Abbreviations: CI, Confidence interval; HR, Hazard ratio; LBW, Low birth weight; SGA, Small for gestational age.

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ABSTRACT

Objective The H1N1 influenza in 2009-10 was declared a pandemic by the WHO. Although numerous studies have examined the risks of pregnancy outcomes in mothers undergoing vaccination against H1N1 influenza, we are unaware of any study examining offspring mortality beyond the first week of life.

Design, setting and participants Prospective population-based cohort study from seven health care regions in Sweden based on vaccinations taking place between October 2, 2009 and November 26, 2010. We linked H1N1 vaccination data with pregnancy and offspring mortality data in 275,500 births of 137,886 mothers. Of these offspring, 41,183 had been exposed to vaccination during fetal life. A primary comparison group consisted of pregnancies of women *not* undergoing vaccination during the same calendar period. In a second comparison, non-exposed siblings to infants prenatally exposed to vaccination were used as controls.

Cox regression estimated adjusted hazard ratios (aHRs) for offspring mortality.

Exposure Pandemrix®, a mono-valent AS03-adjuvanted H1N1 influenza vaccine.

Main outcome measures Offspring mortality, divided according to stillbirth, death on days 0-6 (early neonatal period) and death from day 7 until 4.6 years of age.

Results During follow-up, there were 1,172 stillbirths, 380 early neonatal deaths, and 706 deaths thereafter (total n=2,258). Compared with general population controls, this corresponded to adjusted HRs of 0.83 for stillbirth (95% confidence interval (CI): 0.65 to 1.04), 0.71 for early neonatal death (95%CI: 0.44 to 1.14), and 0.97 for later death (95%CI: 0.69 to 1.36). Using siblings as controls, aHRs were 0.88 for stillbirth (95%CI: 0.59 to 1.30), 0.82 for early neonatal death (0.46 to 1.49), and 0.78 for later death (0.52 to 1.19).

Conclusion Our results indicate that AS03-adjuvanted H1N1 vaccination during pregnancy does not affect offspring mortality.

Keywords: Child, H1N1, vaccination, influenza, offspring

INTRODUCTION

Influenza A(H1N1)pdm09[1 2] was declared as a pandemic influenza by the WHO in mid-2009.[3] Several pandemic vaccines were produced during this time, with Sweden opting for the AS03-adjuvanted monovalent vaccine, Pandemrix®. This vaccine was offered free of charge to all Swedish residents.

Given evidence that pregnant women were especially prone to severe influenza[3,4], vaccination was recommended at any stage of pregnancy. We[4] and others[5-24] have since examined pregnancy and fetal outcomes in mothers undergoing vaccination against H1N1 Most research suggests that H1N1 vaccination has few adverse effects on pregnancy outcomes. In fact, some studies have even found an inverse relationship between H1N1 vaccination and adverse pregnancy outcomes, potentially due to treatment selection bias. Fell *et al* note in their recent systematic review that risk estimates for adverse pregnancy outcomes often move closer to the null after adjusting for potential confounders[25] such as education, income levels, smoking, parity, and comorbidity. However, no study has considered confounding by familial (i.e. genetic and early environmental) factors.

Despite the abundance of research on influenza A(H1N1)pdm09 vaccination and pregnancy outcomes, we are unaware of studies exploring offspring mortality beyond the first week of life (sometimes also included with stillbirths in the joint outcome “perinatal death” [17]).

The primary objective of this population-based cohort study was to explore mortality in offspring of mothers undergoing influenza A(H1N1)pdm09 vaccination. A secondary objective was to examine stillbirth, early neonatal death, and offspring mortality after taking familial factors into account. To

do so we used a sibling-design. A sibling-design is useful if vaccinated women differ systematically from women not opting for vaccination (for instance through being more health-aware which would decrease the risk of complications or for suffering from more comorbidity which would increase the risk of complications).

METHOD

We linked individual data on influenza A(H1N1)pdm09 vaccinations (Pandemrix®[26]) administered in 2009-10 to pregnant women with information of pregnancy and birth characteristics from the Swedish Medical Birth Register. We added offspring mortality data from the Swedish Cause of Death Register. As described in our study on risk of neurological and immune-related diseases in vaccinated individuals[27], we obtained vaccination data from seven Swedish regions (the counties of Kalmar, Östergötland, Stockholm, Värmland, and Norrbotten plus the health care regions of Västra Götaland and Skåne). These regions comprise some 61% of the Swedish population[27].

Databases, registers, and co-variates

In Sweden, Pandemrix vaccinations were given free of charge from October 2009 through 2010. High-risk groups (e.g., pregnant women) were actively encouraged to undergo vaccination and were prioritized for the early batches of the vaccine. Vaccination recording was considered complete in four of the seven regions involved in this study[27]. In these regions, registration of vaccinations was required for cost reimbursements. In the remaining three counties (representing about 13% of the study population: Kalmar, Värmland, and Norrbotten), vaccination registration was performed through a web-based system that required personal informed consent. Because of lack of consent (and thereby lack of the recorded personal identity number), exposure classification (vaccination: yes/no) was not possible in 16-22% of vaccinated individuals in these counties. These individuals were classified as unexposed in the main analyses of the study, but were excluded in a

subsequent sensitivity analysis.

Through the county-specific databases, we obtained data on personal identity number[28], as well as date of vaccination. As opposed to children, in which some individuals received two vaccinations, pregnant women received no more than one vaccination.

To safeguard the integrity of the study participants, personal identity numbers were replaced by unique serial identification numbers before data elaboration.

Participants

We originally retrieved data on 279,999 births (includes siblings) between April 24, 1980 and December 31, 2012, but excluded 1,232 without data in the Medical Birth Register, 3,156 who did not fulfil inclusion criteria (dead or not in study counties before September 30, 2009, or inconsistent migration information), and 111 for other reasons. Thus, the final study sample included 275,500 births (of which 1,203 were stillbirths) of 137,886 women. Characteristics of study participants are presented in Table 1.

Follow-up

In the main analysis, we restricted the study participants (n=121,979) to births after September 30, 2009. These subjects were followed from 22 completed gestational weeks until death or censoring (emigration or end of follow-up, which was May 22, 2014), with separate analysis for stillbirth, early neonatal death, and later death (i.e., deaths from 7 completed days to 4.6 years). For the sibling analysis, we used the whole cohort (279,999), but because comparisons were done within family, only siblings discordant and with at least one event within the family (n=3,801, 1,130, and 2,190) contributed to the analyses of stillbirth, neonatal death and death in the subsequent period.

H1N1 vaccination

The study exposure was vaccination against influenza A(H1N1)pdm09 (Pandemrix®) at any stage of pregnancy.

In all, 93,156 women giving birth during the study period were vaccinated with Pandemrix®, of whom 44% were vaccinated during pregnancy (n=41,183 offspring). Control pregnancies were those for which there was no record of influenza A(H1N1)pdm09 vaccination during pregnancy in a pregnant woman giving birth in any of the seven health care regions of this study. We also divided vaccinations according to pregnancy trimesters of vaccination (1-13 weeks, 14-26 weeks, and 27 weeks until delivery).

Co-variates

Data on covariates were primarily retrieved from the Medical Birth Register[29]. This registry contains information on prenatal and neonatal data on >98% of all births in Sweden since 1973[29]. During the first prenatal visit, commonly occurring at the end of the first trimester, the pregnant women are interviewed and examined by a midwife[30]. The pregnant women are asked about current smoking habits, (0, 1-9, and ≥10 cigarettes per day) and medical, obstetric, and gynaecologic history. Self-reported information about women's height is recorded and women are weighed. We calculated body mass index (BMI) as ([weight in kilograms]/[height in meters squared]), and categorized BMI into four categories: <18.5, 18.5-<25, 25-<30, and ≥30 [31]. Information about parity is collected at the time of delivery (1, 2 and 3+). A small proportion of women had no data on BMI (9.6%) or smoking (4.6%).

Through the government agency Statistics Sweden, we obtained information on mother's country of birth (categorized as born in Sweden or born outside Sweden) and disposable annual income (<25,000 USD or ≥25,000 USD).

Sibling comparisons

Sibling studies take familial factors into account when comparing exposed and unexposed

individuals. From the Medical Birth Register, we identified all siblings of infants prenatally exposed to the mothers' vaccinations during pregnancy. Hence, we were able to compare offspring mortality between children with the same mother according to vaccination exposure. By comparing offspring of the same mother discordant for vaccination exposure, we by design adjusted for genetic and environmental factors shared by the siblings.

Outcome measure

Overall death was the main outcome measure and was examined based on time of occurrence. We specifically studied death during pregnancy (stillbirth from 28 completed gestational weeks until 2008, and from 22 weeks in 2009 and onwards), newborn deaths during the first 6 days life (early neonatal death), and death thereafter (from 7 completed days of life to 4.6 years).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Statistics

All analyses were done in two ways. First, we used all pregnancies ending after September 30, 2009 (start of the vaccination period) as independent observations. Second, we used all pregnancies where vaccination occurred, together with all other pregnancies of the same woman. This latter approach was used in within-family analysis by conditioning on the mother (stratified Cox). Cox regression was used to estimate HRs for stillbirth, early neonatal mortality (days 0-6) and subsequent mortality (beginning on day 7) in vaccinated vs. non-vaccinated women with fetal/infant age as the study time scale, adjusting for mother's age at birth, BMI, parity, smoking,

country of birth, disposable income, and sex of offspring. We found no evidence of non-proportional hazards. In addition, we specifically examined risks of stillbirth, early neonatal death, and offspring mortality according to trimester of vaccination.

For the analysis of stillbirth, the exposure (vaccine during pregnancy or during the trimesters) was time-dependent. We began follow-up at 22 (or 28) gestational weeks. Thus, if the mother was vaccinated before the start of follow-up, the fetus was considered exposed from the start; otherwise, the subject was considered unexposed until the date of vaccination. All data presented in the results section represent adjusted estimates.

Statistical significance was defined as 95% confidence intervals (CIs) for risk estimates not including 1.0. Data were analysed using R statistical software (version 3.1.1).

Ethics

The study was approved by the Research Ethics Committee of Karolinska Institutet (2009/1952-31/4), which deemed that no individual informed consent was required.

RESULTS

Vaccinated mothers tended to be slightly older than non-vaccinated mothers (Table 1). Some 42.3% of vaccinated mothers vs. 48.4% of non-vaccinated mothers were nulliparous. Vaccinated mothers were more often born in Sweden than non-vaccinated mothers. The mean gestational ages at birth were 39.8 vs. 39.7 weeks in vaccinated compared with non-vaccinated mothers. For the offspring mortality analysis, children were followed until a mean age of 4.1 years in the vaccinated cohort and 6.4 years in the non-vaccinated cohort. Among the unexposed pregnancies in siblings (n=39,314), 31,496 (80.1%) took place before the pregnancy exposed to Pandemrix, and 7,818 (19.9%) took place after the index pregnancy.

During pregnancy, there were 1,172 stillbirths, 380 deaths in the early neonatal period, and 706 deaths after the early neonatal period (Table 1). Compared with general population controls, offspring of vaccinated mothers were not at increased risk of stillbirth (adjusted HR=0.83; 95%CI=0.65 to 1.04), early neonatal death (aHR=0.71; 95%CI=0.44 to 1.14), or later death (aHR=0.97; 95%CI=0.69 to 1.36). Using siblings as controls, corresponding HRs were 0.88 (95%CI=0.59 to 1.30), 0.82 (0.46 to 1.49), and 0.78 (0.52 to 1.19) respectively (Table 2). None of the trimester-specific risk estimates was statistically significant after adjustment for potential confounders, except for a decreased risk of stillbirth (-33%) in women who underwent vaccination in the second trimester. However, when siblings were used as controls, this decrease was no longer evident (-23%, p>0.05).

Excluding individuals from the three regions Kalmar, Värmland and Norrbotten did not influence

our risk estimates more than marginally. Among the remaining 37,584 pregnancies exposed to H1N1 vaccination, the HRs of fetal death, early neonatal death and later death were 0.80, 0.76 and 0.88 respectively. Using a sibling approach the HRs for our outcomes were similar to that in our main analysis (0.80, 0.88 and 0.78 respectively).

DISCUSSION

Principal findings

This population-based cohort study found no excess mortality in offspring of women who underwent vaccination against influenza A(H1N1)pdm09 during pregnancy. Consistent with earlier data, no association was found between maternal vaccination and stillbirth or early neonatal mortality[25]. Importantly, the associations between maternal vaccination and risks of stillbirth, early neonatal mortality, and later mortality also remained close to null even when we used sibling controls. Our findings are reassuring in that a large share of Swedish women who were pregnant in 2009-2010 underwent vaccination against influenza A(H1N1)pdm09 despite limited knowledge about potential long-term effects of Pandemrix®[26]. In all, our mortality study included more than 40,000 children exposed to Pandemrix® during fetal life.

Comparison with other studies

This study is one of the largest to date exploring the risk of stillbirth in women vaccinated against influenza A(H1N1)pdm09. Moreover, it is the first study to examine offspring mortality beyond the early neonatal period. A Swedish study with data suggesting that influenza A(H1N1)pdm09 vaccination was greatly under-ascertained[32] (less than 12% of the mothers had a record of vaccination) used almost the same study population as the current study when examining stillbirth. That study found a 23% risk reduction for stillbirth among vaccinated women; we found a 17% non-significant risk reduction compared with the general population. Further, several other large-

scale studies have reported an inverse relationship between maternal vaccination and stillbirth (risk ratios: 0.56[23], 0.66[7], 0.59-0.74[33], 0.77[32], and 0.79[9]), although few of these inverse relationships reached statistical significance. We suspected that the seemingly negative association might be due to selection bias and therefore examined stillbirth using siblings as controls, where the HR increased somewhat (HR=0.88). We conclude that maternal influenza A(H1N1)pdm09 vaccination during pregnancy is unlikely to increase the risk of stillbirth. This conclusion is important as recent data suggests that pregnant women with a clinical diagnosis of influenza are at increased risk of stillbirth[19].

Although experts have proposed a number of mechanisms as to how vaccination might affect pregnancy outcomes (either decrease or increase the risk of adverse pregnancy outcome), we hypothesized that Pandemrix® vaccination would not influence offspring mortality. Early-life mortality is largely influenced by perinatal events, and considering that neither preterm birth nor stillbirth[25] seems to follow upon influenza A(H1N1)pdm09vaccination, we thought it unlikely that offspring mortality would increase after H1N1 vaccination.

We studied offspring mortality according to time of follow-up (0-6 days after birth vs. later). Mortality in the first days of life often differs from later mortality as asphyxia has its predominant effect early in life. However, if there was any protective effect from H1N1 vaccination in offspring, it seems to have had its greatest impact shortly after birth. We believe that the trend towards a protective effect is a result of selection bias of mothers undergoing such vaccination, but a real effect cannot be ruled out considering earlier data showing a protective effect against influenza in offspring of pregnant women undergoing vaccination[34 35] There was no significant association between vaccination in the third trimester and early neonatal death, either in the general population analysis (HR=0.48) or in the sibling analysis (HR=1.24). However, these estimates were based on few cases, and results should be interpreted cautiously.

The neutral risk of offspring mortality beyond the perinatal period is the most novel finding in our paper. As evidenced by the large number of papers on immune-mediated diseases and influenza A(H1N1)pdm09 vaccination, there has been a fear that this vaccination might trigger an immune response. Such a response could take place not only in the mother but potentially also in the fetus. In that regard our findings are comforting. Excess risk was not observed in either the general population control comparison (HR=0.97) or in the sibling analysis (HR=0.78). The lack of adverse pregnancy outcome is consistent with a recent questionnaire study by van der Maas that found no increase in general practitioner-recorded infections during the first year of life in infants exposed to H1N1 vaccination during pregnancy[36].

Strengths and limitations

This study has several strengths. First, we had access to detailed data on vaccination through regional vaccination registers, which precludes recall bias. Second, analyses were adjusted for potential confounders (e.g., sex, parity, smoking, and BMI). Third, we believe that almost all pregnant women in the study area were included in our study. Fourth, Swedish prenatal health care is almost exclusively funded by the public[37], and the influenza A(H1N1)pdm09 vaccination program was free of charge, thereby counteracting selection bias. Furthermore our study is one of the largest studies on influenza A(H1N1)pdm09 vaccination during pregnancy so far and included more than 300 offspring deaths during or after pregnancy. The large statistical power also allowed us to stratify for trimesters.

Among the weaknesses is our lack of data on miscarriage before gestational week 22, and consequently we were unable to study whether this may have influenced the lack of association between H1N1 vaccination and stillbirth. Secondly, were unable to ascertain which mothers had pandemic flu during pregnancy. Neither did we have data on factors influencing the decision to

vaccinate during pregnancy and we cannot rule out that residual confounding influenced our results. Still, our use of sibling controls should control for at least some bias, and importantly the HR for stillbirth was neutral in that analysis.

Conclusion

In conclusion our results suggest that maternal H1N1 vaccination during any trimester of pregnancy has no adverse effect on offspring mortality, during pregnancy, in the early neonatal period or in early childhood.

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JFL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
PS carried out the data analyses under the supervision of CL and JFL.

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Table 1. Study participants characteristics.

Variable	Vaccinated N (%)	Not vaccinated N (%)
All	41,183 (100)	234,317 (100)
Mother's age at birth (years)		
<19	188 (0.5)	2,895 (1.2)
19 - 24	4,016 (9.8)	41,750 (17.8)
25 - 29	10,790 (26.2)	72,335 (30.9)
30-34	15,570 (37.8)	77,173 (32.9)
>35	10,619 (25.8)	40,164 (17.1)
Mother's BMI*		
<18.5	828 (2.0)	5,969 (2.5)
18.5 - <25	24,293 (59.0)	133,481 (57.0)
25 - <30	8,892 (21.6)	49,003 (20.9)
>30	4,208 (10.2)	22,325 (9.5)
Missing data	2,962 (7.2)	23,539 (10.0)
Sex		
Male	21,293 (51.7)	120,641 (51.5)
Female	19,890 (48.3)	113,676 (48.5)
Parity		
0	17,402 (42.3)	113,402 (48.4)
1	16,411 (39.8)	83,356 (35.6)
≥2	7,370 (17.9)	37,559 (16.0)
Smoking*		
Non-smoker	37,825 (91.8)	205,495 (87.7)
1-9 cigarettes/day	1,711 (4.2)	13,009 (5.6)
10+ cigarettes/day	486 (1.2)	4,205 (1.8)
Missing data	1,161 (2.8)	11,608 (5.0)
Mother's birth country		
Sweden	33,353 (81.0)	173,268 (73.9)
Not Sweden	7,830 (19.0)	61,049 (26.1)
Disposable income		
< 25,000 USD	10,396 (25.2)	56,204 (24.0)
> 25,000 USD	30,787 (74.8)	178,113 (76.0)
Status at end of follow-up		
Dead (pregnancy)	115 (0.3)	1,057 (0.5)
Dead (neonatal)†	31 (0.1)	349 (0.1)
Dead (childhood)§	57 (0.1)	649 (0.3)
Alive	40,910 (99.3)	231,668 (98.9)
Emigrated	70 (0.2)	594 (0.3)
Gestational age (weeks), *mean (SD)*	39.8 (1.9)	39.7 (2.0)
Age at end of follow-up, *mean (SD)*	4.1 (0.3)	6.4 (4.0)

* At first visit to the maternal health care.
† Here defined as the first six days alive.
BMI, Body mass index. SD, Standard deviation.
§ From 2nd week after birth and onwards.

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Table 2. H1N1 vaccination during pregnancy and offspring mortality (stillbirth, early neonatal and later death).

	Population		Sibling	
	Hazard Ratio Adjusted for Age (95% CI)	**Hazard Ratio Multivariable-Adjusted (95% CI)†**	**Hazard Ratio Adjusted for Age (95% CI)**	**Hazard Ratio Multivariable-Adjusted (95% CI)†**
Stillbirth				
Overall	0.83 (0.67 to 1.02)	0.83 (0.65 to 1.04)	0.82 (0.59 to 1.15)	0.88 (0.59 to 1.30)
1st trimester	0.91 (0.68 to 1.23)	0.97 (0.72 to 1.33)	1.01 (0.60 to 1.70)	1.09 (0.61 to 1.97)
2nd trimester	0.74 (0.54 to 1.03)	0.67 (0.47 to 0.97)	0.81 (0.46 to 1.44)	0.77 (0.38 to 1.59)
3rd trimester	0.82 (0.53 to 1.26)	0.82 (0.52 to 1.31)	0.59 (0.29 to 1.20)	0.68 (0.31 to 1.53)
Early neonatal death				
Overall	0.71 (0.47 to 1.06)	0.71 (0.44 to 1.14)	0.65 (0.41 to 1.03)	0.82 (0.46 to 1.49)
1st trimester	1.04 (0.61 to 1.77)	0.98 (0.52 to 1.82)	0.82 (0.41 to 1.65)	1.07 (0.43 to 2.67)
2nd trimester	0.57 (0.29 to 1.14)	0.64 (0.31 to 1.34)	0.42 (0.19 to 0.91)	0.53 (0.20 to 1.37)
3rd trimester	0.47 (0.21 to 1.08)	0.48 (0.19 to 1.20)	1.00 (0.35 to 2.86)	1.24 (0.32 to 4.78)
Later death				
Overall	0.81 (0.59 to 1.11)	0.97 (0.69 to 1.36)	0.65 (0.46 to 0.93)	0.78 (0.52 to 1.19)
1st trimester	0.70 (0.42 to 1.16)	0.86 (0.51 to 1.47)	0.46 (0.24 to 0.87)	0.47 (0.22 to 1.01)
2nd trimester	0.91 (0.58 to 1.42)	1.10 (0.69 to 1.76)	0.95 (0.54 to 1.68)	1.44 (0.74 to 2.78)
3rd trimester	0.81 (0.49 to 1.35)	0.93 (0.54 to 1.60)	0.62 (0.33 to 1.19)	0.65 (0.30 to 1.39)

† Adjusted for age (fetal / born), mother's age at birth, body mass index, sex, parity, smoking, country of birth, and disposable income