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Safety of vaccination against influenza A (H1N1) during pregnancy in the Netherlands: results on pregnancy outcomes and infant's health: cross-sectional linkage study

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Objective This study aims to assess the safety of Influenza A(H1N1), vaccination administered during the second and third trimester and containing MF59 and thiomersal (Focetria®), measured by pregnancy outcomes and infant's health.

Design Cross-sectional linkage study.

Setting and sample A sample of pregnant women, eligible for prenatal screening, were invited to participate.

Methods Questionnaire data were linked with the Netherlands Perinatal Registry (n = 1920). Information on infant growth, development (n = 1739) and infection-related contacts with the general practitioner (GP) during the first year of life (n = 1671) was obtained.

Main outcome measures Multivariate logistic regression was used to assess the association between H1N1 vaccination and small-for-gestational-age infant, preterm delivery and a composite adverse outcome, i.e. low Apgar-score, neonatal intensive care unit admission, neonatal resuscitation or perinatal death. Influence of maternal vaccination on growth, development and GP infection-related contact rates were assessed using multivariate linear mixed modelling and multivariate negative binomial regression, respectively.

Results Response rate was 21%. Though we found differences in characteristics between unvaccinated and vaccinated women, in the multivariate analyses no association was found between H1N1 vaccination and small-for-gestational-age (odds ratio [OR] 0.84; 95% confidence interval [95% CI] 0.50–1.43), preterm delivery (OR 0.98; 95% CI 0.59–1.62) and the composite adverse outcome (OR 0.84; 95% CI 0.44–1.60). We found no differences in weight-for-age (−0.05; 95% CI −0.13 to 0.04), length-for-age (−0.01; 95% CI −0.09 to 0.06), head-circumference-for-age (−0.05; 95% CI −0.13 to 0.03), developmental scores (−0.06; 95% CI −0.28 to 0.17) and infection-related GP contact rates (incidence rate ratio 1.07; 95% CI 0.91–1.28) between infants of unvaccinated and vaccinated mothers.

Conclusion Pregnancy outcomes did not differ between H1N1-vaccinated and unvaccinated women. Furthermore, growth, development and GP infection-related contact rates, assessed after the first year of life, were similar in offspring of vaccinated and unvaccinated mothers.

Keywords Infant, influenza, pregnancy, safety, vaccination.

Tweetable abstract No increased risk for adverse pregnancy outcomes and infant's health following influenza vaccination.

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Introduction

In spring 2009 an influenza A (H1N1) pandemic occurred. Influenza during pregnancy increases the risk of hospitalisation due to respiratory complications, especially for women with co-morbidity.[1–3] Furthermore, during the 2009 pandemic, an increased risk of adverse pregnancy outcomes after infection was reported.[4–6] Therefore, the Dutch Health Council advised all pregnant women in the second and third trimester to be vaccinated.[7] A thiomersal-containing vaccine, adjuvanted with MF59 (Focetria®; Sanofi Pasteur MSD, Lyon, France) was used. Until that moment, there were no universal vaccination programmes for healthy pregnant women in the Netherlands.

In 2009, information on the safety of influenza vaccination during pregnancy was scarce and merely based on nonadjuvanted seasonal influenza vaccines. No safety signals were acknowledged in these studies, i.e. no serious adverse events, no differences in adverse pregnancy outcomes or infant hospital admissions, no excess of malformations or childhood malignancies.[8–11]

To date, several studies on the safety of adjuvanted influenza vaccines during pregnancy have been published. None showed an increased risk on adverse pregnancy outcomes.[12–19] The majority of the studies concerned the effect of Pandemrix®, adjuvanted with ASO3. None of the studies included follow up of the offspring up to 1 year of age.

The Centre for Infectious Disease Control of the Netherlands, part of the Dutch National Institute for Public Health and the Environment (RIVM), monitored the determinants of acceptance, coverage and safety of the H1N1 vaccination campaign among pregnant women. Data on acceptance and coverage have been reported previously.[20] The current paper describes and discusses the safety of vaccination with Focetria® during the second and third trimesters of pregnancy. To assess the possible impact of the vaccination, data on pregnancy outcomes and growth, development and infection-related contacts with the general practitioner (GP) of the infants up to 1 year of age were retrieved from three different sources and linked to data of a questionnaire survey.

Methods and materials

Study population and setting

All pregnant women in the Netherlands are offered screening for infectious diseases, i.e. hepatitis B, syphilis and HIV infection, around week 12 of gestation (in any case before the week 15). The Centre for National Population Screening of RIVM is responsible for this screening programme. The Department for Vaccine Supply and Prevention Programmes of RIVM is responsible for data management. Data are registered in a nationwide database. A random sample of nearly 15 000 pregnant women, eligible for vaccination against influenza A (H1N1) in November and December 2009 and known to the Department for Vaccine Supply and Prevention Programmes were asked to participate in a questionnaire study on determinants of acceptance and vaccine coverage.[20] Women who were willing to participate in further research on safety were asked to fill out an additional questionnaire, to give permission to link to the Netherlands Perinatal Registry (PRN),[21] to obtain information on growth and development of the infant from child health care and to ask for infection-related contacts with the GP during the first year of life. Due to higher risks of low birthweight and short gestational age, women with multiple births were excluded.

Medical ethical approval of this study was not necessary because only routinely collected data were used and participants were not subjected to imposed rules or acts. All participants signed written informed consent for the respective study parts. Furthermore, the Board of the PRN approved the study. The latter included approval obtained upon assessment by a privacy commission.

Data collection

The PRN is a joint effort of four professional organisations that provide perinatal care in the Netherlands: Royal Organisation of Midwives in the Netherlands, National Organisation of General Practitioners, Dutch Association of Obstetrics and Gynaecology and Paediatric Association of the Netherlands. PRN covers about 95% of all deliveries. Only pregnancies from 16 weeks onwards are registered in PRN, so information on early abortions is not available. Participating midwives, obstetricians and GPs performing deliveries fill in predefined forms concerning a large number of variables for each birth. Data processing and data cleaning are performed in a systematic way to enhance comparability and enable trend analysis.

Questionnaire data were linked to the database of midwives, obstetricians and paediatricians from PRN based on date of birth of mother and child and four digits of postal code. In this way, forms were combined when multiple obstetric professionals were involved in the care process during pregnancy, delivery or the postpartum period. No other personal data were accessible to the researchers.

Three dichotomous pregnancy outcomes were defined:

1 Small-for-gestational-age, defined as a birthweight below the tenth centile, adjusted for gestational age and based on Dutch averages[22]
2 Preterm delivery, i.e. birth before 37 weeks of gestation
3 A composite indicator for other severe adverse outcomes, including at least one of the following: low Apgar-score (score < 7 at 5 minutes after delivery), admission to Neonatal Intensive Care Unit, resuscitation of the newborn or perinatal death.

Growth and development of infants is monitored by Dutch child healthcare centres, for which attendance amounts to 99%.[23] Growth is subdivided into length, weight and head circumference and recorded according to standardised graphs for Dutch children.[24,25] Development is measured by 'van Wiechen schedule' with age-specific milestones according to the 90th centile for Dutch children.[26] Hereby five aspects are scored, i.e. fine and gross motor function, speech, language and psychosocial aspects. The scores on the developmental instrument were quantified using a developmental score (D-score), based on the Rasch model. A D-score enables a comparison of scores between persons and an evaluation of the developmental velocity within a child.[27]

Data about infection-related contacts of the children within their first year of life were collected through medical records of GPs. Nearly all people living in the Netherlands are registered with a GP. The medical records from GPs contain all relevant medical history, including prescriptions, laboratory results and secondary care information. For each child, we asked the GP for an excerpt including all contacts, i.e. telephone calls, consultations at the office and house visits, during as well as outside working hours, related to temperature or fever, symptoms of an infection of one or more organ systems or prescriptions to treat infectious symptoms. The number of contacts were counted.

Vaccine and vaccination

Pregnant women eligible for vaccination could receive their vaccination at the GP practice. GPs offered these H1N1 vaccinations free of charge from 9 November 2009 onwards. The H1N1 vaccination campaign was finished before Christmas, with only a few people vaccinated in 2010. A two-dose schedule was used with an interval of 3 weeks between the doses. The only vaccine used was Focetria®, delivered as multi-dose containers with thiomersal as a preservative, MF59C.1 as adjuvant and 7.5 μg influenza virus surface antigens of A/California/7/2009 (H1N1)-like virus per dose. In this study, vaccination status was self-reported.

Covariates

All but three covariates were retrieved from the self-reported questionnaires (Table 1). Maternal problems (defined as abnormalities in general medical, gynaecological and obstetric history and obstetric problems during current pregnancy), birthweight and small-for-gestational-age (SGA) infants were retrieved from PRN data. All covariates were chosen based on a plausible or known possible influence on the outcomes.

Statistical analysis

Differences in characteristics of vaccinated and unvaccinated women were tested using Pearson's chi-square test or Fisher's exact test (for dichotomous and categorical variables) or Student's *t*-test (for continuous variables).

Multivariate logistic regression analysis was used to assess the association between H1N1-vaccination and the three defined adverse pregnancy outcomes. To improve comparison of the models for the three outcomes, all models included the same set of possible confounders, i.e. year of birth, country of birth, educational level, self-reported use of alcohol, tobacco and drugs during pregnancy, parity, underlying medical condition as reason for vaccination, maternal problems, H1N1 infection and philosophy of life, e.g. religion, anthroposophy. Associations are presented as odds ratios (ORs) with 95% confidence interval (95% CI).

The *z*-scores, i.e. standard deviation scores, for head-circumference-for-age, length-for-age and weight-for-age were calculated using Dutch references.[22] A *z*-score is computed to determine the outcome of an individual in relation to reference measurements of a comparable population with the same age and sex. The *z*-scores were analysed using a linear mixed effect model, with random intercept and random slope for age. We compared *z*-scores between infants of vaccinated and unvaccinated mothers, and adjusted for birthweight, sex and number of previous pregnancies.

Differences in D-scores between infants of vaccinated and unvaccinated mothers were assessed using a linear mixed effect model with random intercept and random slope for age, adjusted for educational level of the mother and whether or not the mother was born in the Netherlands.

Counts of the total number of infection-related contacts in the first year of life, registered in the medical record of the GP, were analysed using negative binomial regression, adjusted for educational level, country of birth of the mother and SGA infant. Differences in contact rates were expressed as an incidence rate ratio.

Before the study, we estimated that about 2200 pregnant women had to be included to detect an increase in the prevalence of abnormal postnatal growth from 2.5% to 5%, measured through length and weight ($\alpha = 0.05$, $\beta = 0.20$), based on an expected vaccination coverage of 33–50%. Hereby, abnormal growth is defined as length or weight below the 2.5th centile or above the 97.5th centile compared with a reference group of Dutch infants of the same sex and age.

Analyses were performed using SAS version 9.3, *z*-scores for growth were computed using R. In all analyses, a *P*-value < 0.05 was considered statistically significant. Furthermore, unvaccinated mothers and their offspring were set as reference in all analyses.

Results

Study population

Twenty-one per cent of the 14 529 invited women participated in the coverage study, of whom 88% ($n = 2672$) were interested in further studies.[20] In Figure 1, the number of women in each step of the study is presented. Finally, we could link data of 1736 women (85.3% of the 2034 who participated in this study) to the PRN, we obtained data on the growth and development of 1554 children (76.4%) and information on infection-related GP contacts of 1435 children (70.6%).

Of the women who gave permission to use questionnaire data, 66.7% ($n = 1357$) were vaccinated, 32.9% ($n = 669$) received no vaccination and 0.4% ($n = 8$) had an unknown vaccination status.

Table 1. Background characteristics of Influenza A(H1N1)-vaccinated and unvaccinated pregnant women

Background characteristics	Vaccinated* (*n* = 1357); *n* (%)	Not vaccinated (*n* = 669); *n* (%)	*P*-value**
Year of birth			
Before 1970	37 (2.7)	18 (2.7)	<0.0001
1970–74	278 (20.5)	138 (20.6)	
1975–79	618 (45.5)	249 (37.2)	
1980–84	377 (27.8)	216 (32.3)	
1985 or later	47 (3.5)	48 (7.2)	
Country of birth			
The Netherlands	1289 (95.1)	641 (95.8)	0.45
Other country	67 (4.9)	28 (4.2)	
Educational level			
No education or only primary/secondary school	54 (4.0)	39 (5.8)	0.03
Intermediate vocational education	405 (29.9)	222 (33.2)	
Higher vocational education or university	898 (66.2)	408 (61.0)	
First pregnancy			
Yes	545 (40.3)	338 (50.6)	<0.0001
No	809 (59.7)	330 (49.4)	
Underlying medical condition			
Yes	89 (6.6)	22 (3.3)	0.002
No	1268 (93.4)	647 (96.7)	
Self-reported use of alcohol during pregnancy			
Yes	97 (7.2)	35 (5.3)	0.11
No	1250 (92.8)	625 (94.7)	
Self-reported use of drugs during pregnancy			
Yes	2 (0.2)	3 (0.5)	0.16
No	1347 (99.8)	658 (99.5)	
Self-reported smoking during pregnancy			
Yes	57 (4.2)	27 (4.1)	0.87
No	1286 (95.8)	633 (95.9)	
Philosophy of life			
No specific philosophy of life	1152 (90.2)	505 (78.5)	<0.0001
Religious	71 (5.6)	74 (11.5)	
Anthroposophy/homeopathy/alternative medicine/other	54 (4.2)	64 (10.0)	

*Reported to have received at least one vaccination against influenza A (H1N1).
**Pearson's chi-square test or Fisher's exact test.

Vaccinated women were older than unvaccinated women, had a higher educational level, were more often multipara, more frequently had an underlying medical condition as a reason for vaccination and less often reported a religious background or a specific life philosophy such as anthroposophy compared with unvaccinated women (Table 1). There was no difference in country of birth, self-reported use of alcohol or drugs and self-reported smoking during pregnancy.

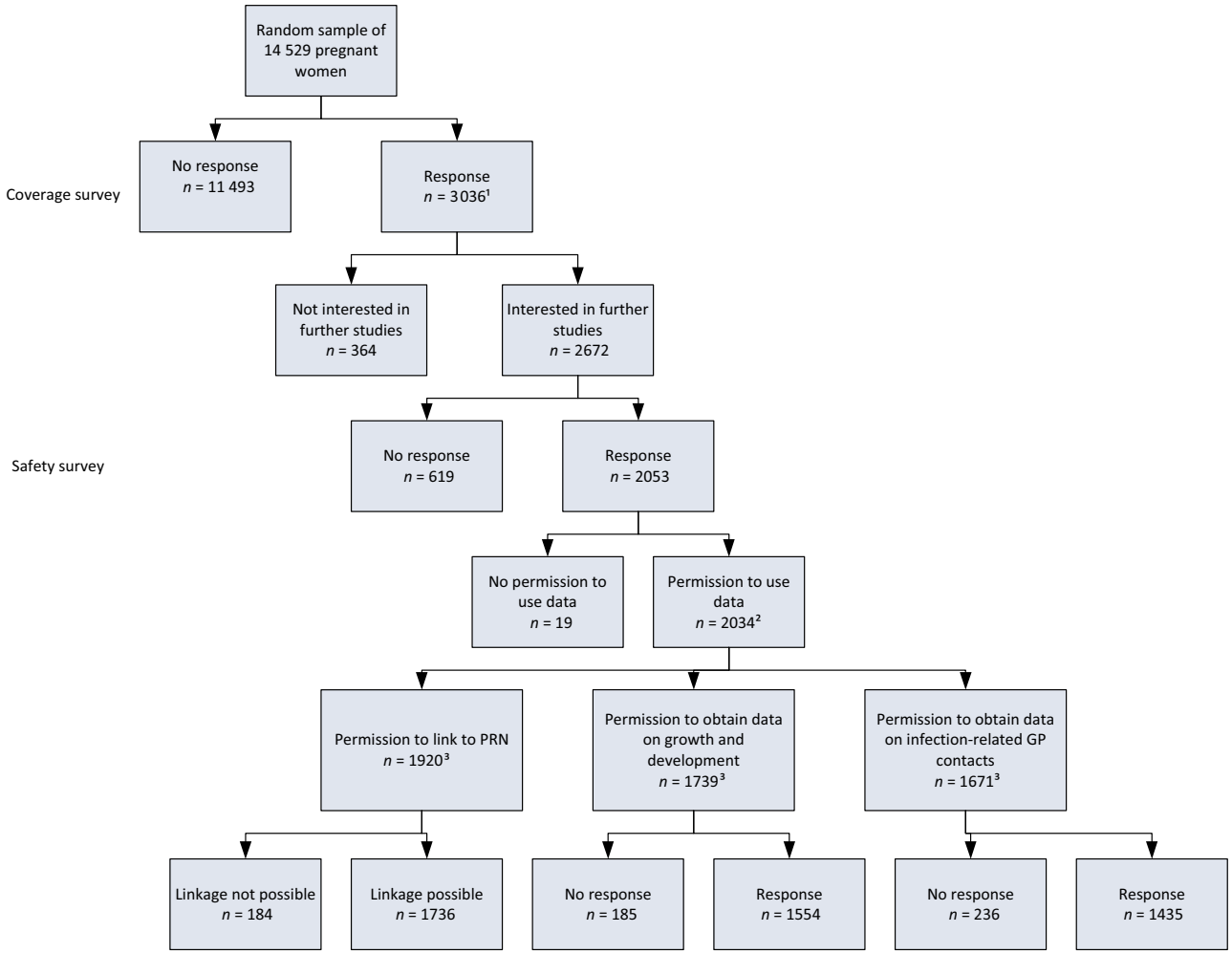
Pregnancy outcomes

Of the 1736 women with data linked to PRN, 1184 women (68%) were vaccinated and 552 (32%) were not. They gave birth to 902 boys and 819 girls. Of 15 infants, the sex was unknown. No maternal deaths were reported.

Logistic regression showed no association between H1N1 vaccination and SGA infants (crude OR 0.81, adjusted OR 0.84; 95% CI 0.50–1.43) (Table 2). Likewise, no increased risk for preterm birth (crude OR 0.95, adjusted OR 0.98; 95% CI 0.59–1.62) nor for the composite outcome (crude OR 1.01, adjusted OR 0.86; 95% CI 0.46–1.64) was found.

Growth and development

We found no statistically significant difference in the *z*-score for weight-for-age between infants of unvaccinated and vaccinated mothers (−0.05; 95% CI −0.13 to 0.04), adjusted for sex, number of infants in the household and birthweight. This indicates that the weight of infants of vaccinated mothers and unvaccinated mothers is distributed similarly compared with a reference group of Dutch infants of the same age and sex. Similar results were found for length-for-age and head-circumference-for-age (*z*-score −0.01 [95% CI −0.09 to 0.06] and −0.05 [95% CI −0.13 to +0.03], respectively).



[1]: 58% reported to have receieved one vaccination, another 5% reported to have had two doses
[2]: 61% reported to have receieved one vaccination, another 6% reported to have had two doses
[3] : 1,656 women gave permission to retrieve data from all three sources.

Figure 1. The identification of participants from the total study population.

Furthermore, we found no statistically significant differences in developmental-scores between infants of vaccinated and unvaccinated mothers (−0.06; 95% CI −0.28 to 0.17), adjusted for educational level and country of birth of the mother.

Infection-related GP contacts

Total number of GP contacts per infant in the first year of life ranged from 0 to 29 (mean 3.4, median 3.0) (Figure 2). In total, 1336 and 3438 GP contacts were reported for infants of unvaccinated women and vaccinated women, respectively. Acute (upper) airway infections were mentioned as reason for the GP contact in 28% and 27% of the contacts of infants of unvaccinated and vaccinated mothers, respectively, followed by acute otitis media (9% and 10%), gastrointestinal complaints (7% and 6%) and fever (7% and 5%). For other diseases, the percentages were lower. Sixty-two hospitalisations were documented.

We found no significant difference in the proportion of infants having contact with their GP for infection-related symptoms between vaccinated and unvaccinated mothers. The incidence rate ratio was 1.07 (95% CI 0.91–1.28), adjusted for SGA and educational level and country of birth of the mother.

Discussion

Main findings

To our knowledge this is the first study about the safety of MF59-adjuvanted H1N1 vaccination, not only assessing pregnancy outcomes, but also the possible impact on the

Table 2. Logistic regression analysis of vaccination against influenza A (H1N1) and small-for-gestational-age infant, preterm birth and a composite adverse outcome (including at least one of the following: Apgar score <7, neonatal intensive care unit (NICU) admission, neonatal resuscitation, perinatal death)

	Small-for-gestational-age				Preterm birth (gestational age <37 weeks)				Composite adverse outcome			
	Total *n*	SGA*n* (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)	Total *n*	Preterm*n* (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)	Total *n*	Comp. outcome *n* (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Vaccinated												
No	528	27 (5.1)	Ref		523	26 (5.0)	Ref		528	16** (6.1)	Ref	
Yes	1123	46 (4.1)	0.81 (0.50–1.33)	0.84 (0.50–1.43)	1104	54 (4.9)	0.95 (0.59–1.54)	0.98 (0.59–1.62)	1123	32*** (4.1)	1.01 (0.54–1.88)	0.86 (0.46–1.64)

*Adjusted for year of birth, country of birth, educational level, use of alcohol, tobacco and drugs during pregnancy, parity, underlying medical condition as reason for vaccination, maternal problems, H1N1-infection and life philosophy.
**Three infants with low Apgar score, 12 infants admitted to NICU, no perinatal death, three infants resuscitated.
***Eleven infants with low Apgar score, 19 infants admitted to NICU, three perinatal deaths, ten infants resuscitated.

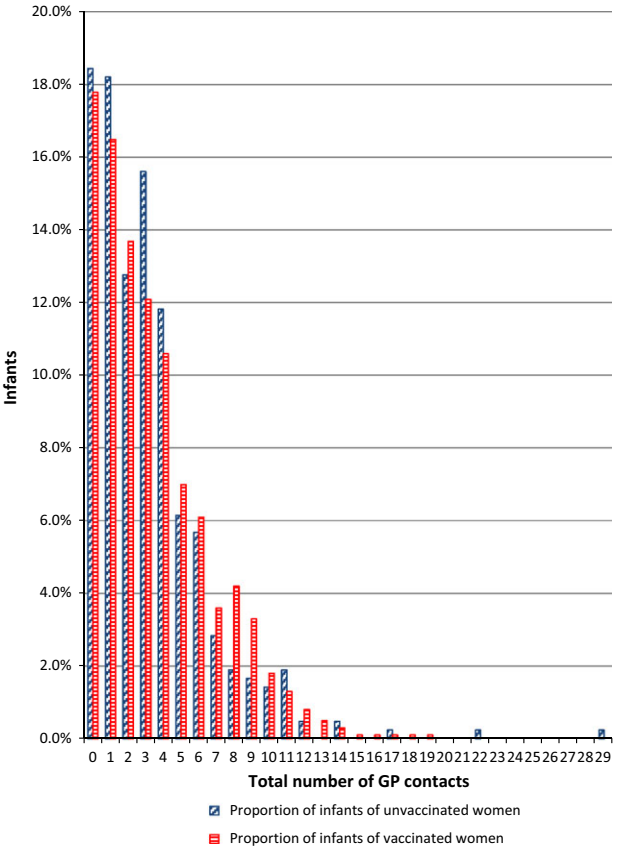


Figure 2. Frequencies of infant GP contacts of unvaccinated and vaccinated mothers during the first year of life.

infant's health during the first year of life. We found no increased risk of MF59-adjuvanted H1N1 vaccination in the second and third trimesters of pregnancy on adverse pregnancy outcomes measured by preterm birth, SGA and a composite outcome including rare but severe adverse outcomes. Furthermore, we found no negative impact on growth (i.e. head circumference, length and weight), development and GP contacts for infection-related reasons during the first year of life.

Strengths and limitations

This study has several strengths. Data collection and data entry were performed independent of the vaccination status. Data were merged with the original questionnaire data after data entry in the respective study databases and only the original questionnaire contained information on self-reported maternal vaccination status.

Furthermore, vaccinated and unvaccinated mothers were recruited simultaneously, so they were exposed to the same environmental influences, e.g. influenza infection.

Due to the extensive questionnaire survey, we were able to adjust for several well-known confounders, e.g. smoking.

Finally, PRN data are cleaned and coded using standardised methods, resulting in good comparability of pregnancy outcomes.

Several limitations must be acknowledged. The participants of this study were not fully representative of all Dutch pregnant women. In the first questionnaire survey on coverage and acceptance there was a low and selective response.[20] Respondents were slightly older and less likely to have a due date in November 2009 compared with non-respondents. Furthermore, respondents were more frequently born in the Netherlands and had a higher educational level than assessed in nationwide surveys. Although we cannot exclude the possibility, this may have affected our results, it is unlikely that any selective response would have had a large impact on the association between H1N1 vaccination during pregnancy and the studied outcomes, because our results are comparable with the results of other studies, including a nonselective, nationwide cohort study, performed in Denmark.[14–16,19,28,29] Furthermore, our analysis of adverse pregnancy outcomes showed significant effects of several well-known risk factors with the outcome measures, e.g. smoking (data not shown). Finally, frequencies of preterm birth, support of pregnancy and delivery by midwife or gynaecologist in our study were comparable with results of the PRN data in general, enclosing 95% of the pregnancies in the Netherlands.[30]

Likewise, the number of participants did not amount to the number assessed in the sample size calculation, but we think a higher number of participants will not change our conclusion, because our results are in line with results of other studies and frequencies of important variables are comparable with frequencies, found in other databases, as already mentioned above.

Timing of vaccination could not be included as a possible confounder, because of the presence of unvaccinated women in our study. Stratifying vaccinated women by trimester of vaccination and comparing each subset with the group of unvaccinated women would reduce the power of the study, so we decided not to do this.

Our results are not generalisable to women, vaccinated in their first trimester, because in the Netherlands, only women in their second and third trimester were eligible for vaccination.

The estimated coverage among pregnant women was 63%.[20] In the subset of women, participating in the follow-up study on safety, 67% of the women reported to be vaccinated, i.e. an overrepresentation of vaccinated mothers. This might have influenced our results. However, we were able to adjust for a large number of possible confounders, so we think this influence will be limited.

Misclassification due to mistakes in data entry can have influenced our results. However, this misclassification is probably nondifferential, because during data collection and data entry the vaccination status of the participant was unknown.

Furthermore, in the Netherlands, registries do not include a personal unique identifier. Therefore, linking PRN and questionnaire data was only possible based on date of birth of the mother and child, and postal code. This might have led to inaccurate linking in the case of identical linking variables in two or more records. This misclassification is probably nondifferential, because information on vaccination status was unknown during linkage. Furthermore, we tried to prevent these inaccuracies by manually reviewing overlapping records and by also using infants' birthweight as a linking variable in these records, if the exact weight was available in the questionnaire data.

The H1N1 vaccination campaign was implemented during the pandemic. In fact, 66 pregnant women in our study reported to have had pandemic flu. In most cases, the exact date of onset was unknown and no laboratory confirmation was performed. Forty-eight of these women also reported H1N1 vaccination. Analysis without the inclusion of these 66 women did not change our results (data not shown). Therefore, we think the influence of this was limited.

Finally, the vaccination status was self-reported. The occurrence of recall bias is possible when pregnant women were unaware of their vaccination status. However, we believe this risk is small, because there was strong debate about vaccination during pregnancy in our country.

Interpretation

Our results are in line with previous studies on the safety of adjuvanted H1N1 vaccines, administered during pregnancy.[14–16,19,28,29] All of these studies included at least low birthweight, preterm birth or SGA in their analysis, and in none of these studies was an increased risk of these outcomes found following vaccination.

Our results on infant's growth fit well with the findings of normal birthweight and normal duration of pregnancy after H1N1 vaccination during pregnancy, because following intrauterine noxious exposure, abnormal postnatal growth may not occur without foetal growth impairment.[31,32] Furthermore, the similar development of infants of vaccinated and unvaccinated mothers we found is consistent with the fact that no excess of congenital anomalies was found in any study.[14,19,28,29] Frequent or long-term hospitalisation due to congenital anomalies may result in impaired (motor) development.[33,34] In these cases, often a catch up in development is seen after discharge. Furthermore, some congenital anomalies and impaired development have a common aetiology, e.g. genetic syndromes, exposure to noxious agents, congenital brain anomalies.[35–38] However, normal development in the first year of life does not imply normal development later in life.[39]

Conclusion

Our study showed no increased risk for several adverse pregnancy outcomes and infant health during the first year of life following administration of an influenza A (H1N1) vaccine, adjuvanted with MF59 and preserved with thiomersal, during the second and third trimesters of pregnancy. These findings are reassuring for public and professionals and may help the decision-making process on maternal immunisation in case of a new pandemic and possible other infectious diseases, which can be prevented by maternal vaccination. Further research regarding the safety, effectiveness and acceptability of maternal immunisation is needed to further cover gaps in knowledge.

Disclosure of interests

None of the authors has a conflict of interest to disclose.

Contribution to authorship

NvdM, AvL, JK and HdM designed the study. NvdM, JDE and AvL contributed to data collection. NvdM, JDE, JK, AvL, MK and HdM contributed to data analysis. NvdM wrote the manuscript; JDE, JK, AvL, MK and HdM critically revised subsequent versions and approved the final version. NvdM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Details of ethics approval

Medical ethics approval of this study was not necessary because only routinely collected data were used and participants were not imposed a specific deed. All participants signed written informed consent for the respective study parts. Furthermore, the Board of the PRN approved the study. The latter included approval obtained upon assessment by a privacy commission.

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