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2009 A/H1N1 influenza vaccination in pregnancy: uptake and pregnancy outcomes - a historical cohort study.

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2009 A/H1N1 Influenza Vaccination in Pregnancy: Uptake and Pregnancy Outcomes- a retrospective cohort study

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Condensation

Pandemic influenza vaccine uptake is influenced by maternal sociodemographic factors; 2009 A/H1N1 vaccination in pregnancy is not associated with adverse pregnancy outcomes.

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Abstract

Objectives

To describe the uptake of 2009 A/H1N1 Influenza vaccination among pregnant women and determine if vaccination was associated with adverse pregnancy outcomes.

Study Design

A retrospective cohort study was performed using booking, Delivery Suite and neonatal discharge records from the Coombe Women and Infants University Hospital. Singleton deliveries to women pregnant before (December 2008-September 2009) and during the pandemic (December 2009-September 2010) were included.

Information on vaccination status and type of vaccine was collected on admission to the Delivery Suite. Logistic regression analyses were used to determine maternal characteristics associated with vaccination. Pregnancy outcomes were compared for vaccinated and unvaccinated women, with adjustment for differing maternal characteristics. Outcomes included vaccination status, preterm birth, size for gestational age, neonatal intensive care admission, congenital anomalies and perinatal death.

Results

Of 6894 women pregnant during the pandemic, 2996 (43.5%) reported vaccination at delivery. In the early weeks of the vaccination programme rates of over 70% were achieved. Of those vaccinated, 246 (8.2%), 1709 (57.0%) and 1034 (34.5%) were vaccinated in the first, second and third trimesters respectively. Vaccination was less likely in younger age groups, those who were not in the professional/manager/employer socioeconomic group, women from Eastern Europe, Africa and Asia/Middle East, those who reported an unplanned pregnancy, women who booked late for antenatal care and recipients of publicly-funded obstetric care. Irish nationality was associated with reporting vaccination. There was no association between vaccination during pregnancy and adverse pregnancy outcomes.

Conclusion

2009 A/H1N1 Influenza vaccination uptake was influenced by maternal sociodemographic factors. High vaccination uptake can be achieved in a pandemic situation. Future public health campaigns should provide clear information on vaccination safety in pregnancy, ensure consistent vaccination recommendations from healthcare professionals and provide easy access to vaccination in order to optimise uptake rates in subgroups of the population who less likely to be vaccinated. There was no association between vaccination and adverse pregnancy outcomes.

Keywords

2009 A/H1N1 Influenza; vaccine; pregnancy; uptake; congenital anomaly; perinatal death.

Introduction

Pandemic 2009 A/H1N1 Influenza infection appeared to increase the risk of severe maternal morbidity and mortality and was associated with adverse pregnancy outcomes including fetal death. (1-4) Previous pandemics also demonstrated the risk of serious adverse maternal and fetal outcomes. (5) In order to reduce the risk of such adverse outcomes vaccinations against pandemic 2009 A/H1N1 Influenza were licensed and recommended for use during pregnancy. (6) In Ireland two vaccines were commercially available and used in the national immunisation campaign: Pandemrix®, an egg-derived vaccine containing thiomersal and the AS03 adjuvant (DL-α-tocopherol, squalene and polysorbate); and Celvapan®, a cell-line-derived, thiomersal free, non-adjuvanted alternative.

Seasonal influenza vaccines have been administered to pregnant women since the late 1950s,(7) and the US Advisory Committee on Immunization Practices (ACIP) has, since 2004, encouraged pregnant women to be vaccinated against seasonal influenza regardless of gestation. (8) Uptake rates of 2009 A/H1N1 Influenza vaccine varied internationally during the pandemic with studies reporting rates in pregnant women from as low as 4.7% to as high as 85%. (9-11) Variations in international recommendations relating to the optimal timing of vaccination in pregnancy, the selection of non-adjuvanted vaccines for pregnant women and the need for seasonal influenza vaccination in pregnancy led to media commentaries, speculation on vaccine safety and public anxiety.

Available data support the use of the inactivated influenza vaccine during all stages of pregnancy, particularly for women with medical conditions that may increase the risk of complications. Reassuring pharmacoepidemiological studies have indicated that 2009 A/H1N1 Influenza vaccination is not associated with adverse pregnancy outcomes including fetal death, preterm birth and congenital anomalies. (12-17)

Vaccination may have reduced the risk of influenza-related fetal death during the pandemic. (12)

It is essential that extensive data are available on pregnancy outcomes after gestational vaccine exposure in order to inform decisions on vaccination by pregnant women and health professionals, particularly during a pandemic situation. It is also important to study the determinants of vaccination uptake in pregnant women in a variety of settings, given the regional variations that have been previously reported. (18) The main aims of this study are to describe the uptake of 2009 A/H1N1 Influenza vaccination in pregnant women during the pandemic, to determine maternal characteristics associated with vaccine uptake, and to determine if there is an association between vaccination and adverse pregnancy outcomes.

Materials and Methods

The Irish Pandemic Flu Vaccination Programme began in early November 2009 and ended on the 31st of March 2010. (19) In the initial phase high risk groups, including pregnant women, were offered prioritised access to the vaccine.

Data on maternal characteristics, medical and obstetric history and perinatal outcomes were extracted from electronic hospital records at the Coombe Women and Infants University Hospital in Dublin for all singleton deliveries during the study period. Data on vaccination status was recorded at delivery from the beginning of December 2009. The following questions were added to the delivery suite admission form:

(1) H1N1 vaccine this pregnancy? (Yes/No)

(2) When given (1st dose) (1st trimester, 2nd trimester, 3rd trimester).

(3) Vaccine used? (Celvapan 1 dose, Celvapan 2 doses, Pandemrix, Unknown)

Preterm and very preterm deliveries were defined as delivery prior to 37 and 32 weeks gestation respectively. Small for gestational age was defined as a birthweight determined to be less than the 10th centile customised for maternal weight, height, gestation and infant sex. (20) Congenital anomalies were ascertained from Delivery Suite or Neonatal Unit electronic records.

Descriptive statistics were used as appropriate to describe maternal characteristics of vaccinated and unvaccinated women. Univariable logistic regression analyses were used to determine odds ratios and 95% confidence intervals for associations between maternal characteristics and vaccination. Cases with missing data were excluded from the logistic regression analyses. The levels of missing data for each maternal characteristic and pregnancy outcome are indicated in Table 1 and Table 2.

Pregnancy outcomes were compared between vaccine-exposed women delivering between December 2009 and September 2010 and two comparison groups. The first comparison group included women delivering from the beginning of December 2009 to the end of September 2010 who reported that they had not been vaccinated at the time of delivery (unvaccinated group). The second comparison group included women delivering from the beginning of December 2008 to the end of September 2009, representing a time period prior to the mass vaccination programme and the main wave of the pandemic (prevaccination group). Univariable and multivariable logistic regression analyses were used to examine the association between vaccination and adverse perinatal outcomes. The multivariable analysis included adjustment for age band at delivery, socioeconomic group, region, planning of pregnancy, booking gestation, public obstetric care and smoking in pregnancy.

A separate univariable logistic regression analysis was carried out to determine if vaccination was associated with congenital anomalies after first trimester exposure with comparison to the unvaccinated group.

Results

Vaccine Uptake

Of 6894 women delivering between the beginning of December 2009 and the end of the following September, 2996 women (43.5%) reported vaccination at delivery. The temporal distribution of vaccination during pregnancy is represented in figure 1. Vaccination in the first, second and third trimesters was reported by 246 (8.2%), 1709 (57.0%) and 1034 (34.5%) vaccinated women, respectively. Celvapan® was received by 1692 (56.5%) women, with approximately half receiving a single dose and half receiving two. A single dose of Pandemrix® was received by 698 (23.3%) women, with a further 606 (20.2%) women unsure of the specific vaccine used.

Maternal characteristics of vaccinated and unvaccinated women are outlined in table 1. Compared with women in the 25-29 age group, those between 30-39 years were more likely to report vaccination. Vaccination was most likely in the professional, manager and employer socioeconomic group compared to all other groupings. There were regional variations in vaccination uptake with women from Eastern Europe less likely to report vaccination than those from Western Europe (odds ratio 0.21, 95% Confidence Interval 0.17-0.25). Women from Africa and Asia/Middle East were also less likely to report vaccination. Irish nationality was associated with reporting vaccination (OR 2.25, 95% CI 2.01-2.51). Women who reported an unplanned pregnancy were less likely to be vaccinated. Those booking after 20 weeks were less likely to be vaccinated (OR 0.49, 95% CI 0.39-0.62) compared to those booking between 12 and 20 weeks' gestation. Women who received privately-funded obstetric care were more likely to report vaccination (OR 1.43, 95% CI 1.25-1.63).

Maternal and perinatal outcomes for the vaccinated and unvaccinated groups are compared in table 2. Adverse perinatal outcomes did not appear to differ significantly between the vaccinated group and the two

comparison groups. In the unadjusted analyses, vaccinated women were less likely to have an elective caesarean section than the unvaccinated group. Preterm birth (<37 and <32 weeks) was also less likely in the vaccinated women. Adjustment for maternal characteristics that differed significantly between the vaccinated and unvaccinated groups with multivariable logistic regression analyses did not alter the results.

There were nine congenital anomalies among 246 pregnancies where women reported vaccination in the first trimester and 110 among 3897 pregnancies in unvaccinated women (3.7% vs. 2.8%; OR 1.31, 95% CI 0.65-2.61). The congenital anomalies recorded for the nine neonates were: duplication of left ureter (history of duplicate kidneys in siblings), atrophic right kidney (maternal history of atrophic kidney also), unspecified chromosomal anomaly, mild pyelectasis on antenatal ultrasound, subcutaneous dermoid cyst, hydronephrosis on antenatal ultrasound, bilateral hydrocele, albinism and cardiomyopathy (maternal cardiomyopathy also).

Comment

Main Findings

This study demonstrated that 42% of women delivering between December 2009 and September 2010 had received at least one dose of pandemic 2009 A/H1N1 Influenza vaccine, with vaccination rates of over 70% in the weeks after the initiation of the vaccination programme. Of the women with known vaccine type, the majority (70.7%) received the cell-line-derived, thiomersal free, non-adjuvanted product Celvapan®. Women who were less likely to be vaccinated included those in younger age groups, those who were not in the professional/manager/employer socioeconomic group, women from Eastern Europe, Africa and Asia/Middle East, women who booked late for antenatal care, those who reported an unplanned pregnancy and those who received publicly-funded obstetric care. Vaccination was not associated with adverse pregnancy outcomes.

Strengths and Limitations

This study was conducted in a large tertiary referral maternity hospital that delivers approximately 9,000 babies annually. Data on maternal characteristics, medical history, vaccination status and pregnancy outcomes were routinely collected by midwives using structured computer-guided and paper questionnaires. Data were available on a diverse group of women from a broad range of socioeconomic groupings. Virtually all deliveries during the study period were included in the analysis, reducing the risk of selection bias. This study also provided information on both adjuvanted and unadjuvanted vaccines. The study results are likely to be generalisable to women receiving antenatal care in similar hospital settings worldwide, though international variations in vaccine uptake are likely.

This study was limited by the inclusion of only one maternity hospital. Current constraints imposed by the Irish Data Protection Act precluded a planned study including the three main Dublin maternity hospitals which deliver 4 in 10 Irish babies. Pregnancy outcomes were ascertained after information on vaccination status was collected, this may have potentially led to biased assessment of outcomes, however there is no evidence to suggest that this occurred. The study was also limited by the constraint of ascertainment of vaccination status at delivery as this prevented any analysis of the relationship between vaccination and early pregnancy loss. Reliance on maternal self-report of vaccination status, vaccine used and timing of vaccination is a potential limitation, however the high profile nature of the pandemic vaccination recommendations meant that most women knew this information. Congenital anomalies were ascertained from routine hospital records up to the time of hospital discharge. There was limited recording of clinical details of anomalies and it is possible that misclassification led to an underestimation of congenital anomalies for all neonates. Although multivariable logistic regression was used to adjust

for differing maternal characteristics between the comparison groups, it is possible that residual confounding remained. This residual confounding may have explained the apparent differences in the elective caesarean section rate between the vaccinated and unvaccinated groups.

Interpretation

There are a number of factors that may have an impact on vaccination uptake rates in the pregnant population. Maternal characteristics associated with vaccination include working outside the home, being multiparous and having a higher level of education. (21) Other factors include the safety concerns of both patients and healthcare workers and also a lack of recommendation of vaccination by medical professionals.(22) A US survey of postpartum women, which reported a vaccination rate of 34%, indicated that the strongest determinants of vaccination were awareness of vaccine safety and health professional recommendations. (23) Some studies identified that Pandemic 2009 A/H1N1 Influenza vaccination was actually offered to a minority of women during pregnancy. (24, 25) Maternal co-morbidities have also been demonstrated to affect the likelihood of vaccination along with regional variations in uptake. (18)

Several similar studies in a variety of international settings have reported uptake rates in pregnancy below 15%. (10, 21, 22, 26) Vaccine availability issues early in the pandemic may have reduced uptake in some studies. Higher rates of 37 to 85% have been reported in other studies from the US and UK. (27-29) In a Dutch online survey with a 20.6% response rate, 63% of pregnant women reported vaccination. (30) An EU survey reported that for pregnant women, Ireland had the second highest vaccination coverage at 32% after the Netherlands at 58%. (31) In line with the findings of this study, vaccination was much less likely in Eastern European countries. Low uptake of the vaccine in pregnancy has also been reported in an Australian study. (32)

The higher estimates from some patient surveys may be caused by sampling bias. Uptake rates will also vary between studies depending on the time period included. In this study, vaccination rates of up to 70% were achieved in women delivering in the weeks after the initiation of the vaccination campaign. These uptake rates may be explained by clear public health messages given in antenatal clinics along with specific vaccination clinics run in the hospital to coincide with antenatal clinics. Vaccination was also available through national vaccination programmes run in the community by public health services.

This study adds to previous findings of regional variations in vaccination uptake. (18, 31) Maternal characteristics associated with not being vaccinated were similar in several international studies. A Canadian study also reported variations in vaccination rates related to maternal age, socio-economic status and late booking.(33) A French study had similar findings with higher vaccination rates in women who were older, employed and born in France.(34)

Previous studies support the current findings of no association between pandemic 2009 A/H1N1 Influenza vaccination in pregnancy and adverse pregnancy outcomes including fetal death, preterm birth and congenital anomalies. (12-17) One previous study noted an association between vaccination and a marginal risk reduction for caesarean section. (17)

Conclusion

This study demonstrates that high influenza vaccine uptake rates can be achieved for pregnant women in a pandemic situation. Future public health campaigns should provide clear information on vaccination safety in pregnancy, ensure consistent advice and vaccination recommendations from healthcare professionals and provide easy access to vaccination e.g. through integration with antenatal care to optimise uptake rates in subgroups of the population who less likely to be vaccinated.

Reassuring data from geographically diverse locations on the relationship between maternal vaccination and pregnancy outcomes will aid future vaccination campaigns. This wealth of safety data will attenuate public uncertainty about vaccine safety in pregnancy. The available data may also improve uptake rates in pregnant women in future pandemics.

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Contribution to authorship: BC proposed the study initially and was responsible for study design along with UR, ME and FM; BC, UR and NM were responsible for acquisition and analysis of data; all authors were involved in drafting the article, revising it and final approval for publication.

Details of ethics approval: The study was approved by the Hospital's Research Ethics Committee on 16th May 2012 (Study No. 3-2012).

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Table 1. Maternal Characteristics among vaccinated and unvaccinated Pregnancies

	N=6894	Vaccinated n=2996 (43.5%)	Unvaccinated n=3898 (56.5%)	OR	95% CI
Age at delivery	6894				
<20 years		97 (37.7)	160 (62.3)	0.92	0.70-1.21
20-24 years		353 (40.3)	522 (59.7)	1.03	0.87-1.22
25-29 years		686 (39.6)	1045 (60.4)	1	-
30-34 years		1015 (44.9)	1248 (55.1)	1.24	1.09-1.41
35-39 years		719 (48.8)	753 (51.2)	1.45	1.26-1.67
>40 years		126 (42.6)	170 (57.4)	1.13	0.88-1.45
Socioeconomic group	6888				
Home duties		481 (37.1)	815 (62.9)	0.61	0.52-0.70
Professional/Manager /Employer		910 (49.3)	934 (50.7)	1	-
Non-Manual		1115 (44.2)	1406 (55.8)	0.81	0.72-0.92
Manual		110 (34.4)	210 (65.6)	0.54	0.42-0.69
Unemployed		240 (42.9)	319 (57.1)	0.77	0.64-0.93
Non-classifiable		140 (40.2)	208 (59.8)	0.69	0.55-0.87
Nationality- Irish	6838				
Yes		2352 (49.2)	2431 (50.8)	1	-
No		618 (30.1)	1437 (69.9)	0.44	0.40-0.49
Region	6838				
Western Europe		2460 (48.6)	2598 (51.4)	1	-
Eastern Europe		144 (16.6)	724 (83.4)	0.21	0.17-0.25
Africa		128 (39.1)	199 (60.9)	0.68	0.54-0.85
South America		16 (50.0)	16 (50.0)	1.05	0.53-2.11
North America		14 (53.8)	12 (46.2)	1.23	0.57-2.67
Asia/Middle East		201 (39.4)	309 (60.6)	0.69	0.57-0.83
Australia & New Zealand		7 (41.2)	10 (58.8)	0.74	0.28-1.94
Married	6792				
Yes		1815 (43.4)	2365 (56.6)	1	-
No		1140 (43.6)	1472 (56.4)	1.00	0.91-1.11
Nulliparous	6894				
Yes		1248 (42.8)	1669 (57.2)	1	-
No		1748 (44.0)	2229 (56.0)	1.04	0.95-1.15
Planned pregnancy	6850				
Yes		2055 (44.6)	2557 (55.4)	1	-
No		934 (41.7)	1304 (58.3)	0.89	0.80-0.99
Booking gestation (weeks)	6832				
< 12 weeks		1317 (46.9)	1493 (53.1)	1.18	1.06-1.30
12 - 20 weeks		1547 (42.8)	2065 (57.2)	1	-
> 20 weeks		110 (26.8)	300 (73.2)	0.49	0.39-0.62
Publicly-funded obstetric care	6894				
Yes		2444 (43.5)	3366 (57.9)	1	-
No		552 (50.9)	532 (49.1)	1.43	1.25-1.63
Smoked During Pregnancy	6891				
No		2527 (43.6)	3270 (56.4)	1	-
Yes		469 (42.9)	625 (57.1)	0.97	0.85-1.10

Table 2. Maternal & Perinatal Outcomes among Vaccinated and Unvaccinated Pregnancies

	n=13938	Vaccinated n=2996	Unvaccinated n=3898	Pre-vaccination n=7044	OR[1]	95% CI	OR[2]	95% CI
Mode of Delivery	13938							
SVD		1768 (59.0)	2220 (57.0)	4105 (58.3)	1	-	1	-
Elective LSCS		208 (6.9)	496 (12.7)	760 (10.8)	0.53	0.44-0.63	0.64	0.54-0.75
Emergency LSCS		420 (14.0)	548 (14.1)	919 (13.0)	0.96	0.83-1.11	1.06	0.93-1.21
Forceps		247 (8.2)	296 (7.6)	522 (7.4)	1.05	0.88-1.26	1.10	0.93-1.29
Ventouse		353 (11.8)	338 (8.7)	738 (10.5)	1.31	1.12-1.54	1.11	0.97-1.28
Preterm birth < 37 weeks	13824	141 (4.7)	252 (6.5)	371 (5.3)	0.71	0.58-0.88	0.89	0.73-1.08
Spontaneous Birth < 37 weeks	13824	73 (2.5)	127 (3.3)	198 (2.8)	0.74	0.55-0.99	0.86	0.66-1.13
Very preterm birth < 32 weeks	13824	26 (0.9)	60 (1.6)	73 (1.0)	0.56	0.35-0.89	0.84	0.53-1.31
Spontaneous Birth < 32 weeks	13824	15 (0.5)	25 (0.6)	30 (0.4)	0.78	0.41-1.48	1.17	0.63-2.19
Small for gestational age < 10th centile†	13824	368 (12.4)	485 (12.6)	862 (12.3)	0.98	0.85-1.13	1.00	0.88-1.14
Apgar score <3 at 1 minute	13911	27 (0.9)	42 (1.1)	57 (0.8)	0.83	0.51-1.35	1.11	0.70-1.76
Apgar score <7 at 5 minutes	13853	21 (0.7)	33 (0.9)	50 (0.7)	0.82	0.47-1.43	0.98	0.59-1.64
Admitted to neonatal unit	13938	507 (16.9)	652 (16.7)	942 (13.4)	1.01	0.89-1.15	1.32	1.17-1.48
Congenital anomaly	13938	66 (2.2)	110 (2.8)	181 (2.6)	0.78	0.57-1.05	0.85	0.64-1.14
Perinatal Death*	13938	11 (0.4)	22 (0.6)	39 (0.6)	0.65	0.31-1.34	0.66	0.34-1.29

[1] Vaccinated versus unvaccinated (Unadjusted odds ratio)

[2] Vaccinated versus pre-vaccination (Unadjusted odds ratio)

[†] Birth weight centiles were calculated using GROW-Centile, a customised weight centile calculator

* includes stillbirths and neonatal deaths. Stillbirth was defined as delivery of a baby showing no signs of life at or after 24 weeks gestation. Neonatal death was defined as the death of a baby within the first seven days of life.