Official Title

Influenza Vaccination Effectiveness of a Quadrivalent Inactivated Vaccine in Pregnant Women and Young Infants (Aged 6 months and Below) During Influenza Season 2019-2020

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Statistical analysis

Women were excluded from the statistical analysis for the following reasons that occurred before the onset of influenza season: decision to withdraw from the study, loss to follow-up, post-partum influenza vaccination (cocooning), pregnancy discontinuation, spontaneous abortion, perinatal death. Women were followed for the entire influenza season, regardless of onset of influenza or ILI. The analysis was restricted to the influenza season. The primary outcome of the study was influenza onset in pregnant women. Secondary outcomes were the onset of influenza in their infants and the onset of ILI, ARI, febrile episode, pneumonia, healthcare seeking, hospitalization, use antibiotics and use of antivirals in pregnant women and their infants. Categorical and continuous variables were compared between vaccinated and unvaccinated groups using the x^2 test and T-test, respectively. Logistic regression analysis was conducted in order to identify factors significantly associated with a history of influenza vaccination in 2019-2020. Odds ratio (OR) and confidence intervals (CIs) were estimated. We have used a Bayesian model selection for logistic regression models with random intercept. The primary outcome of interest was to estimate the average rate of influenza for each group (vaccinated versus unvaccinated group). Our data was a 2 by 2 cross-tabulated data arising from two binary variables with possible values 0 or 1. The first variable was whether a pregnant woman has been vaccinated (value =1) or not (value =0). The second variable was the age group of the pregnant woman. The first group consisted of pregnant women aged less than 32 years (value =0) or not (value=1). We compared the vaccinated pregnant women group with the group of non-vaccinated pregnant women to model the proportion of effectiveness that is the event that a pregnant woman had influenza. We used the Bayesian beta-binomial model due to data heterogeneity because of a large number of

zeros were observed. Given this heterogeneity assumption, a Bayesian hierarchical random-effects model was used to analyze the data. The assumption of our model was that the number of individuals y_j responding to influenza vaccination is binomially distributed as:

$y_j \sim$Binomial (p_j, n_j),

where the success rate (p_j) was the probability of influenza onset in mothers and n_j was the number of individuals in the jth group. We note that there are only 2 groups (j=1,2),: the vaccinated and the not vaccinated groups. The probability (p_j) itself follows a beta distribution with parameters (a_j, b_j). Non-informative distributions priors distributions were placed on the parameters of the beta distributions. P-values of 0.05 or less were considered statistically significant. IVE against influenza was estimated as follows: [1 – (incidence rate of influenza in vaccinated women/incidence rate of influenza in unvaccinated women)] x 100 [11]. The statistical analysis was conducted using R 3.6 (R Foundation for Statistical Computing).

Results

A total of 949 pregnant women were enrolled in the study (Figure 1). Of them, 94 women were excluded from the analysis because of the following reasons: lost to follow-up or decision to withdraw from the study (65 women), post-partum influenza vaccination (cocooning) (25 women), spontaneous abortion (3 women), and perinatal death (1 woman). Therefore, 855 pregnant women were included in the analysis. Their mean age was 32.9 years (range: 18-45 years) and their mean gestational age at enrollment was 23.3 weeks (range: 3-39 weeks).

Of the 855 pregnant women, 525 (61.4%) were vaccinated against influenza and 330 (38.6%) refused vaccination. No serious adverse event occurred. Pregnant women with a history of influenza vaccination the past (2018-2019) season were more likely to get vaccinated against influenza in 2019-2020 compared to women with no history of vaccination (91.8% versus 55.1%, p-value<0.001). In the logistic regression analysis the following variables were significantly associated with a history of influenza vaccination in 2019-2020: lower gestational age (OR: 0.998; CI: 0.998-0.999), influenza vaccination the past season (OR: 8.8; CI: 4.7-16.2), and no smoking during pregnancy (OR: 0.6; CI: 0.4-0.9).

Estimation of IVE in pregnant women

Of the 855 pregnant women included in the analysis, 636 women were still pregnant during the 2019-2020 influenza season and comprised the study group for the estimation of IVE in pregnancy. Of them, 406 women (63.8%) were vaccinated against influenza and 230 (36.2%) refused vaccination. Table 1 shows their characteristics by influenza vaccination status.

Twelve of the 636 pregnant women tested positive for influenza (8 cases of influenza A/H3N2, 2 cases of A/H1N1 and 2 cases of influenza B). Table 2 summarizes their morbidity by influenza vaccination status. The incidence of influenza differed between vaccinated women (6/406; 1.47%) and unvaccinated women (6/230; 2.6%), however the difference was not statistically significant. Similarly, higher rates of febrile episode, ILI, pneumonia, healthcare seeking, hospitalization, use of antibiotics and antivirals were noted in the unvaccinated group compared to the vaccinated group, however none of these differences reached statistical significance (Table 2). The IVE of QIV against influenza was 43.5% for pregnant women during 2019-2020 in Greece. The IVE of QIV against influenza was 43.5% (95% CI: 28.4%-55.6%) for pregnant women during 2019-2020 in Greece.

According to the regression model the age was not a predictor of influenza onset in the sample of pregnant women. Influenza vaccination of pregnant women reduced their logit to develop influenza by -4.2 (95% CI -3,7 -4,7), which indicates that influenza vaccination added a statistically significant protection to pregnant women.

Estimation of IVE in infants

A total of 474 infants were born before or during the 2019-2020 influenza season and constituted the group for the estimation of IVE in infants. Their mean birth weight was 3189 g (range: 630-4650 g) and their mean gestational age was 39.1 weeks (range: 28-42 weeks). There were 281 (59.3%) infants whose mothers were vaccinated during pregnancy and 193 (40.7%) infants of unvaccinated mothers. The unvaccinated mothers had a mean gestational age of 31.2 weeks at enrollment compared to a mean gestational age of 28.3 weeks of vaccinated mothers (p-value

<0.001); no other significant difference was noted between the two groups (data not shown).

Overall, 8 of the 474 infants tested positive for influenza (5 cases of influenza A/H3N2, 2 cases of influenza A/H1N1 and 1 of influenza B). Table 3 summarizes their morbidity by maternal influenza vaccination status. Infants of unvaccinated mothers more often developed influenza, febrile episodes, ILI, ARI, AOM and pneumonia and had increased rates of healthcare seeking, hospitalization, use of antibiotics and use of antiviral agents compared to infants whose mothers were vaccinated, however these differences reached statistical significance only for ARI and use of antiviral agents (p-values=0.012 and 0.036, respectively). The IVE against influenza for infants was estimated at 31.4% in 2019-2020. The IVE against influenza for infants was estimated at 31.4% (95% CI: 4%-51%) in 2019-2020.

According to the regression model the age of pregnant women was not a predictor of influenza onset in the sample of young infants. Additionally the influenza vaccination of pregnant women reduced the logit of their infants to develop influenza by -4.2 (95% CI -3.6, -4.9), which indicates that influenza vaccination during pregnancy added a statistically significant protection to young infants.

Table 1. Characteristics of pregnant women (n=636) by influenza vaccination status

Characteristic	Vaccinated n=406 (%)	Unvaccinated n=230 (%)	P-value
Mean age, years (range)	33.1 (21-45)	32.3 (18-45)	0.055
Mean gestational age, weeks (range)	19.3 (3-39)	21.6 (3-39)	0.003
Underlying disease	49 (12.2)	32 (14.0)	0.512
Influenza vaccination the past season	94 (23.2)	14 (6.1)	<0.001
Mean no. of cohabitants (range)	1.7 (0-8)	1.8 (0-8)	0.147
Children <5 years	161 (39.8)	79 (34.5)	0.190
Mean no. of children <5 years (range)	0.5 (0-3)	0.4 (0-3)	0.325
No smoking during pregnancy	350 (93.1)	173 (84.0)	0.001
Smoking during pregnancy	26 (6.9)	33 (16.0)	

Table 2. Morbidity (%) of pregnant women (n=636) by influenza vaccination status

Type of morbidity	Vaccinated n = 406 (%)	Unvaccinated n = 230 (%)	P-value
Influenza*	6 (1.5)	6 (2.6)	0.314
Febrile episode	17 (4.2)	13 (5.7)	0.402
ARI	115 (28.3)	50 (21.7)	0.069
ILI	11 (2.7)	11 (4.8)	0.169
Pneumonia	2 (0.5)	4 (1.7)	0.118
Healthcare seeking	5 (1.2)	5 (2.2)	0.359
Hospitalization	0 (0.0)	1 (0.4)	0.184
Use of antibiotics	11 (2.7)	7 (3.0)	0.807
Use of antivirals	3 (0.7)	4 (1.7)	0.245

* laboratory-confirmed influenza

ARI: acute respiratory infection; ILI: influenza-like illness

Table 3. Morbidity (%) of infants (n=474) by maternal influenza vaccination status

Type of morbidity	Vaccinated n = 281 (%)	Unvaccinated n = 193 (%)	P-value
Influenza*	4 (1.4)	4 (2.1)	0.59
Febrile episode	7 (2.5)	8 (4.1)	0.312
ARI	17 (6.0)	27 (14.0)	0.012
ILI	6 (2.1)	6 (3.1)	0.507
AOM	1 (0.3)	2 (1.0)	0.358
Pneumonia	0 (0.0)	1 (0.5)	0.227
Healthcare seeking	6 (2.1)	10 (5.2)	0.144
Hospitalization	0 (0.0)	1 (0.5)	0.277
Use of antibiotics	4 (1.4)	5 (2.6)	0.360
Use of antivirals	0 (0.0)	3 (1.6)	0.036

* laboratory-confirmed influenza

ARI: acute respiratory infection; ILI: influenza-like illness; AOM: acute otitis media

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